REV.0

JULY 8, 2010

INFORMATION PACKET

AMERICAN KRATOM ASSOCIATION

ABOUT US

Established in 2014, the American Kratom Association is committed to restoring full consumer access to kratom and to preserve and protect the freedom of consumers in the United States to make their own choices on their well-being and maintaining a healthy lifestyle. The American Kratom Association is a Colorado-registered non-profit corporation in good standing, operating as a 501 c(4). Through the services of its Executive Director and a 3rd-party CPA, the AKA ensures its compliance with both State and Federal regulations through timely internal financial reconciliations and strict Board-adopted conduct policies. We are committed to bringing confidence for each donor that their money is being spent wisely.

OUR VISION

The American Kratom Association was formed in 2014 and officially launched in 2015, to protect the right of all Americans to use the natural botanical Kratom for improved health and well-being. Kratom (Mitragyna speciosa) is a natural analgesic which has been used for hundreds of years to safely alleviate pain, combat fatigue and help with the effects of anxiety and depression. Unfortunately, the spread of misinformation, both scientific and anecdotal, about Kratom has created a challenging regulatory environment. The American Kratom Association was formed to organize and represent a community of responsible consumers, provide the public with clarification surrounding matters of health and wellness where Kratom could play an important role, educate lawmakers and regulators and support scientific research efforts.

OUR MISSION

On behalf of the growing numbers of Kratom users the American Kratom Association works to help protect their ability to use Kratom for the purposes of improved health & well-being.

The American Kratom Association has 5 main goals:

Support Consumers. We believe many political and private entities don't make the needs of the consumer and constituents a priority. Our goal is to change that.

Educate. Kratom has many beneficial purposes and is an all-natural alternative. Our goal is to educate all Americans - from potential consumers to regulators and everyone in between.

Amplify. We represent thousands of Americans that each have a story to tell. We believe the current environment in the United States often does not listen to individual voices and together we will make our voice heard.

Global Awareness. We hope to demonstrate responsible use and practical knowledge other countries may study when considering Kratom legislation.

Protect Natural Resources. Kratom is a precious natural resource. We support and advocate for sustainable harvesting techniques and reforestation efforts.

FINANCIALS

Introduction

At the American Kratom Association (AKA), we feel very strongly that people who contribute to a non-profit organization have the right to know how their money is being spent. With our mission being to protect the rights of individuals to consume kratom for improved health and well-being, we work hard to make sure every dollar is spent wisely.

Allocation of Expenses

We are proud that the vast majority of contributions go toward activities that help keep kratom legal. The AKA hired one of the top law firms in the country, an experienced lobbying team, and a public relations firm that all helped to push back the DEA and defeat anti-kratom legislation across the country.

Our administrative costs this past year were one of the lowest in the industry and we are committed to continuing to run an efficient organization.

Financial Management

The AKA has brought in a team of experienced individuals with a strong business and organizational management background to ensure that every dollar is properly accounted for and tracked. In addition, regular financial reports are produced to ensure transparency and accountability.

Through a robust management team, our goal is to provide the utmost confidence for every contributor.

How we fund our mission

Funding to keep kratom legal comes from individual donors and from organizations whose interested in supporting our mission. We believe strongly in developing long-lasting partnerships with our contributors.

OUR TEAM

Dave Herman, Chairman of AKA Board

With a history of working in the non-profit space, Dave brings to the Board a wealth of experience and a track record of success. After 25 years as a Hotel Executive and Mortgage and Investment banker, Dave retired and began working in the nonprofit arena.

Dave previously worked with a large 501c (4) nonprofit corporation, including serving as Executive Director and National Spokesperson. His experience includes previously testifying before the Congressional Energy and Commerce, Health subcommittee as an expert witness for the Prescription Drug addition to Medicare. His speaking experience includes Nationwide Television, Regional Television, National Public Radio and Newspaper Editorial Board presentation and press conferences.

Dave has also served in various senior management roles including: Chairman and CEO for a large 501c (3) nonprofit corporation, board member for the Patient Advisory Board for Genentech, member of the Novartis Power of Partnering group, and he also worked on patient advocacy programs with Alcon Labs.

Paul Kemp, Vice Chairman

As a resident of Waldport, Oregon, Kemp began his career as a freelance writer, real estate investor and entrepreneur. Starting in 1990, Kemp worked to build the Oakridge, OR, Chamber of Commerce and served as president of that organization twice and as Chamber manager from 1992-1995.

Kemp also served as grant writer, helping the community of Oakridge to re-brand itself as a recreational destination. In conjunction with helping the development of Oakridge, Kemp served on the Board of Directors of the Convention & Visitors Association of Lane County, Oregon (CVALCO.org) which is now EugeneCascadesCoast.org. More recently, Kemp worked in the tourism industry at the Overleaf Lodge on the Oregon Coast until 2015, when he semi-retired to write professionally and devote much of his time to the AKA, where he is a founding board member and currently, vice-chairman of the board and CIO.

While working on his upcoming book, Kemp has published many articles, mostly describing the many uses kratom and trying to dispel the myth about the botanical.

William Robin, Chief Technology Officer

Born in the United Kingdom and now residing in West Palm Beach, Florida, William “Will” Robin is a software engineer and solutions architect working for a large international company. Robin specializes in developing and implementing strategic technological plans and managing software and hardware development teams.

With the ability to develop software in 10 languages, Robin previously developed software solutions and served as an adviser to one of America’s largest independent media companies (Olympusat). Throughout his career, Robin has handled major projects for websites, apps and tech services firms.

Robin joined the AKA board following its inception in 2014 and addresses the day-to-day tech requirements of the organization.

Peter Candland, Executive Director

Peter Candland is the Executive Director of AKA. Mr. Candland brings an extensive business background and is tasked to oversee the AKA contractors, managing day-to-day activities, and providing guidance for the overall strategic plan for the organization. Mr. Candland brings the knowledge necessary to ensure financial compliance with the IRS and that every dollar received is spent accomplishing the mission of the AKA.

Angela Ross, Treasurer and Secretary of the Board

As part of her nearly quarter of a century of business experience, Angela Ross worked in sales and marketing for over 10 years at an international manufacturing company based in Ohio. Ross started out her career at a database marketing firm, where she handled client relations for 14 years.

Ross has committed herself full-time to help manage the day to day operations of the American Kratom Association, where she also serves a board member.

Ross resides in Ohio’s Cuyahoga County, which, with 500 overdose deaths in 2016 alone, is ground zero for the national opioid epidemic. Ross has served witness to that epidemic and advocates for the many recovering opiate addicts whose lives have been made better by the botanical kratom.

Susan Ash, Founder & Spokesperson

Susan Ash is the founder of the American Kratom Association. Passionate about government and the political process, Ash worked on the 2008 and 2012 Obama for President campaigns.

A native of Virginia, Ash began her professional career 27 years ago, in the US National Park Service. She continued her work in the environmental field, leading forest preservation and policy preservation efforts in the Western U.S. Ash has dedicated much of her career to philanthropic and advocacy efforts, holding numerous leadership roles while also chairing and serving on the boards of such organizations as the Audubon Society of Portland and the Virginia-based Keep Norfolk Beautiful nonprofit.

Ash earned a Bachelor of Science in Public Communications from Old Dominion University and a Master of Science in Forestry from the University of Missouri-Columbia. Ash consumes the botanical kratom regularly to manage symptoms of a chronic illness, and is a proud advocate for her fellow consumers.

Chris Bake, Board Member

Chris Bake began his career working for CSB Marketing and Management Corporation, specializing in direct marketing activities in the Washington DC area. After 16 years with the CSB organization, Chris entered the nutritional arena through Nutrition for Life.

While at Nutrition for Life, Chris became a strong advocate for non-traditional treatments and medicines, traveling around the world exploring different options for family members with serious illnesses. Chris believes deeply in the freedom of individuals to make their own decisions on their well-being.

For the last 15 years, Chris has built a successful organization as an independent Venture Capital Consultant. Chris brings to the Board extensive experience in organizational fundraising, partnership development, and creative solution development.

Robin Graham, Board Member

Robin Graham has provided extensive training services to a variety of organizations, including the American Red Cross and private security firms.

She holds degrees in data processing, business management and accounting.

A resident of Lewiston, Montana, Graham spent over a decade working with the American Red Cross in a variety of capacities that include fundraising, community outreach and disaster deployment. In addition to her tenure with the American Red Cross, Graham has worked with other nonprofits for more than a quarter of a century, including the Girl Scouts of America.

Bobby F. Kennedy III, Board Member

Robert (Bobby) Kennedy III has been a longtime activist for Democracy, Environmentalism and Transparency in film and media. Bobby brings a unique perspective that will greatly enhance the ability of the AKA to communicate our message and develop strategies that will enable us to reach a larger audience of advocates.

Bobby has spent his career as a film maker, activist, and champion of protecting individual freedoms.

Michael D. Ostrolenk, Board Member

Michael D. Ostrolenk is co-founder of the Liberty Coalition and the Medical Privacy Coalition and served as program manager for the Natural Health Research Institute. He also served as an analyst for the Association of American Physicians and Surgeons and Citizens for Health.

With these positions as well as many others, Michael has an extensive background and strong record of accomplishments in working with the heath industry and government policies, as he successfully convened initiatives to protect liberty, privacy and more.

Michael holds a MA from John F. Kennedy University and has a BA in Government.

AMERICAN KRATOM ASSOCIATION

AKA
Kratom Fact Sheet

The American Kratom Association, is a non-profit organization formed in 2014 by consumers to protect our right to use kratom as a natural, herbal remedy. We do not profit off the sale of kratom; we owe our quality of lives to it. We have several hundred dues-paying members, a network of 2,400 supporters and over 15,000 Facebook and Twitter followers. We are mostly professionals in our 30's, 40's and 50's -- productive members of society managing illnesses and ailments with kratom.

What is Kratom?

Kratom, *Mitragyna speciosa*, is a tree in the coffee family native to Southeast Asia. Its leaves have been consumed in countries like Thailand and Malaysia for well over 500 years. Farmers and laborers traditionally used it in much the same way as coffee – to boost energy and increase productivity. Today Americans use kratom for things like fatigue, pain, depression, anxiety, PTSD, to ease themselves off opiates and to help manage addiction. Kratom is now consumed in the U.S. just like other herbal supplements and remedies, as more and more people look to natural alternatives to manage their health.

What Kratom is not

Kratom is not new. Kratom is not synthetic. Kratom is not an opiate. It is not dangerous when used responsibly, nor is it highly addictive. The media likes to report, among other inaccuracies, that kratom causes hallucinations, paranoia and/or psychosis when there is no scientific or even anecdotal evidence to back such claims. It was not banned in its native Thailand because it's dangerous, but because it was cutting into the government's opium tax.

Kratom has proven medicinal use

Many studies have shown kratom to have positive medicinal benefits. A 2015 study in Dove Press Journal concluded kratom merits further study to develop its medical benefits, as a better opioid substitute, with fewer lethal side effects, or as an effective pain killer. A 2014 study in the Journal of Pacific Cancer Prevention even concluded the benefits of the leaves are not limited to analgesic properties but could be promising antioxidant and anti-cancer compounds. It's no wonder at least 4 patents have been filed on the primary constituents of the plant!

Adverse reactions from kratom are not pervasive

The National Forensic Laboratory Information System, the DEA database that collects information from forensic labs throughout the country shows kratom appears in just a fraction of one percent of all reports for substances in 2013 (173 times) and 2014 (137 times). Contrast that with an over the counter pain reliever like acetaminophen (the main ingredient in Tylenol) which sends 78,000 people to the Emergency Room each year.

Kratom is not habit forming when used responsibly

Kratom is non-habit forming, unless taken in high doses for extended periods of time. Users may experience dependence (similar to caffeine dependence) and discomfort on stopping excessive, daily use abruptly. Taken in excess it will cause nausea and vomiting; its own built-in safety mechanism.

How people consume Kratom

Traditionally leaves were chewed or steeped into a tea. Today the leaves are dried and powered to be used in dietary supplements, as a tea, taken in straight powder form or in capsules.

Legality of Kratom

Kratom is legal in all states but Indiana, Tennessee, Wisconsin, Vermont and Arkansas. These states have laws based largely on the misconception that kratom is a synthetic drug. The Wisconsin Controlled Substances Board is in the process of removing its ban. Dr. Alan Bloom, Board member and professor of pharmacology and toxicology said recently, “There’s no scientific basis for it” (classifying kratom as a dangerous drug). The Florida State Senate recently recognized kratom has medicinal value and changed a bill attempting to outlaw it to allow adults to consume, possess and sell it.

Florida Department of Law Enforcement Report

The Florida Department of Law Enforcement (FDLE) released a December 2015 report titled Kratom - Mitragyna speciosa, The Impact to Florida and found, “Kratom does not currently constitute a significant risk to the safety and welfare of Florida residents. Additionally, the report sites that the Florida Department of Health found there are no pervasive health issues can be attributed to the ingestion Kratom products in Florida.”

Noteworthy quotes

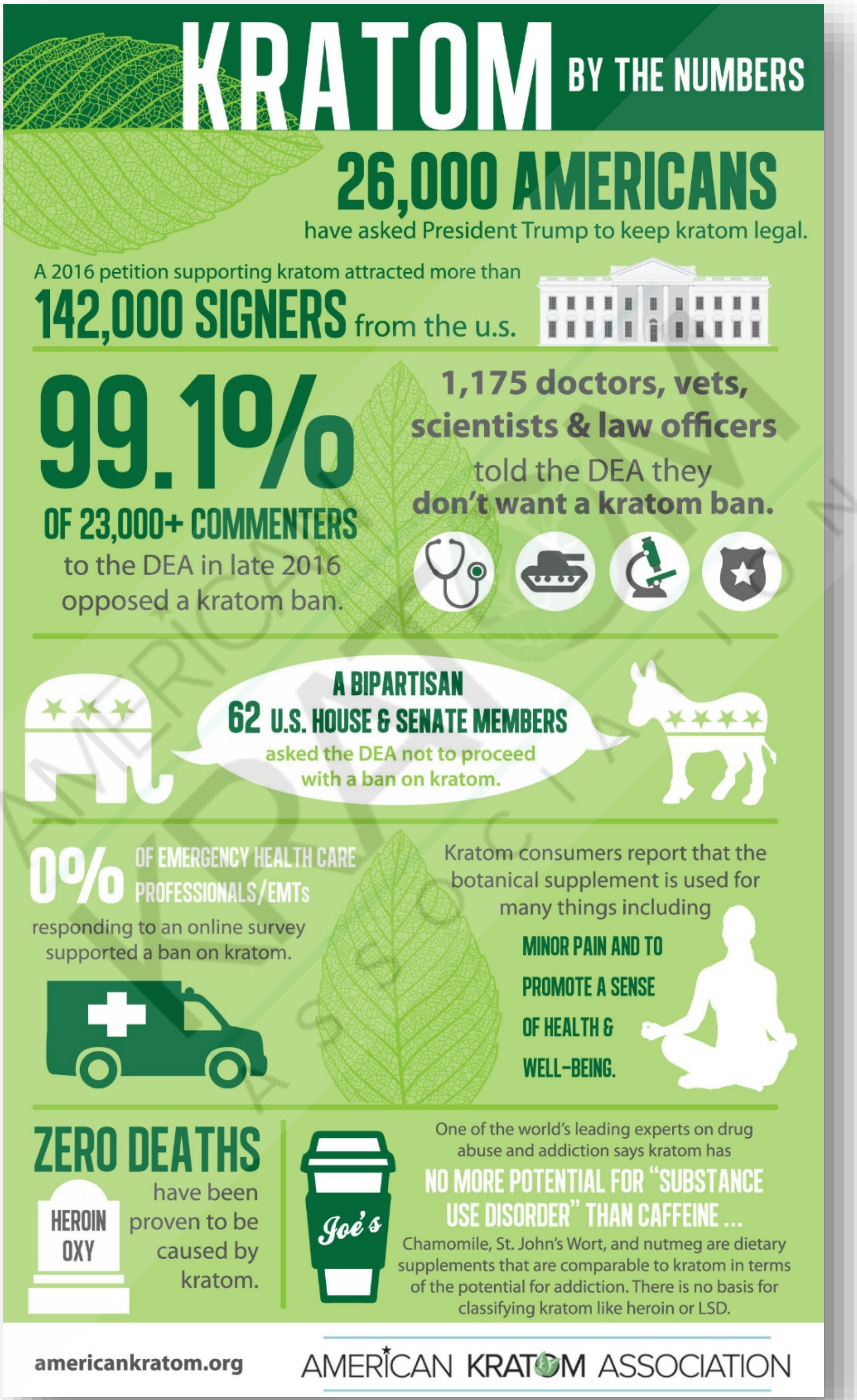
Ryan Estevez, MD, Tampa Bay, Florida: “In recent years, kratom has been widely misrepresented as dangerous and without medical value. These disturbing labels overlook the fact that valuable remedies and dietary supplements derived from kratom benefit lives. Kratom, in fact, is not a drug at all: It is a plant derivative no more dangerous than a cup of coffee.”

Jane Maxwell, Research Professor at the Addiction Research Institute at the University of Texas: When asked about the impact and presence of kratom across the U.S., “It’s pretty minor.”

Conclusion

In the words of Dr. Christopher McCurdy, head researcher at the University of Mississippi (where kratom has most recently been studied in the U.S.): “Based on the information available in the scientific literature, we know that Kratom has been utilized for centuries by people in Thailand, without stigma associated with its use. In traditional medicine, Kratom has been used as an antidiarrheal and as a treatment for opioid dependence. Although there are suggestions that Kratom has a risk of addiction, there is no solid scientific evidence available to support or refute this idea.”

Kratom is safely relieving mental and physical suffering in the lives of adults across America. We support further scientific study of the plant, and oppose legislation that will turn responsible kratom users into criminals.



KRATOM BY THE NUMBERS

26,000 AMERICANS have asked President Trump to keep kratom legal.

A 2016 petition supporting kratom attracted more than **142,000 SIGNERS** from the u.s.

99.1% OF 23,000+ COMMENTERS to the DEA in late 2016 opposed a kratom ban.

1,175 doctors, vets, scientists & law officers told the DEA they **don't want a kratom ban.**

A BIPARTISAN **62** U.S. HOUSE & SENATE MEMBERS asked the DEA not to proceed with a ban on kratom.

0% OF EMERGENCY HEALTH CARE PROFESSIONALS/EMTs responding to an online survey supported a ban on kratom.

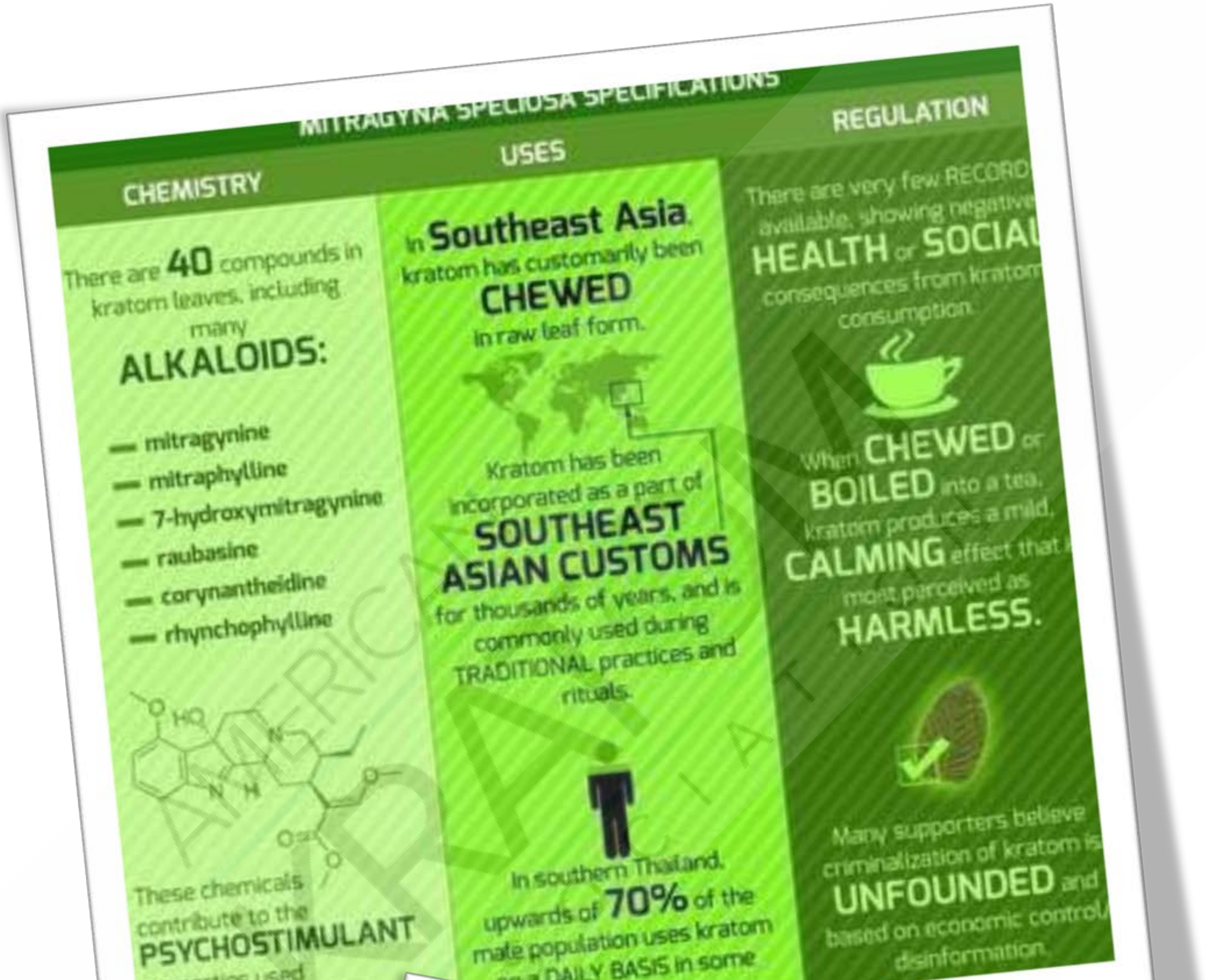
Kratom consumers report that the botanical supplement is used for many things including MINOR PAIN AND TO PROMOTE A SENSE OF HEALTH & WELL-BEING.

ZERO DEATHS have been proven to be caused by kratom.

One of the world's leading experts on drug abuse and addiction says kratom has NO MORE POTENTIAL FOR "SUBSTANCE USE DISORDER" THAN CAFFEINE ... Chamomile, St. John's Wort, and nutmeg are dietary supplements that are comparable to kratom in terms of the potential for addiction. There is no basis for classifying kratom like heroin or LSD.

americankratom.org

AMERICAN KRATOM ASSOCIATION



MITRAGYNA SPECIOSA SPECIFICATIONS

CHEMISTRY

There are **40** compounds in kratom leaves, including many **ALKALOIDS:**

- mitragynine
- mitraphylline
- 7-hydroxymitragynine
- raubasine
- corynantheidine
- rhynchophylline

These chemicals contribute to the **PSYCHOSTIMULANT** properties used to ameliorat ents.

USES

In **Southeast Asia**, kratom has customarily been **CHEWED** in raw leaf form.

Kratom has been incorporated as a part of **SOUTHEAST ASIAN CUSTOMS** for thousands of years, and is commonly used during TRADITIONAL practices and rituals.

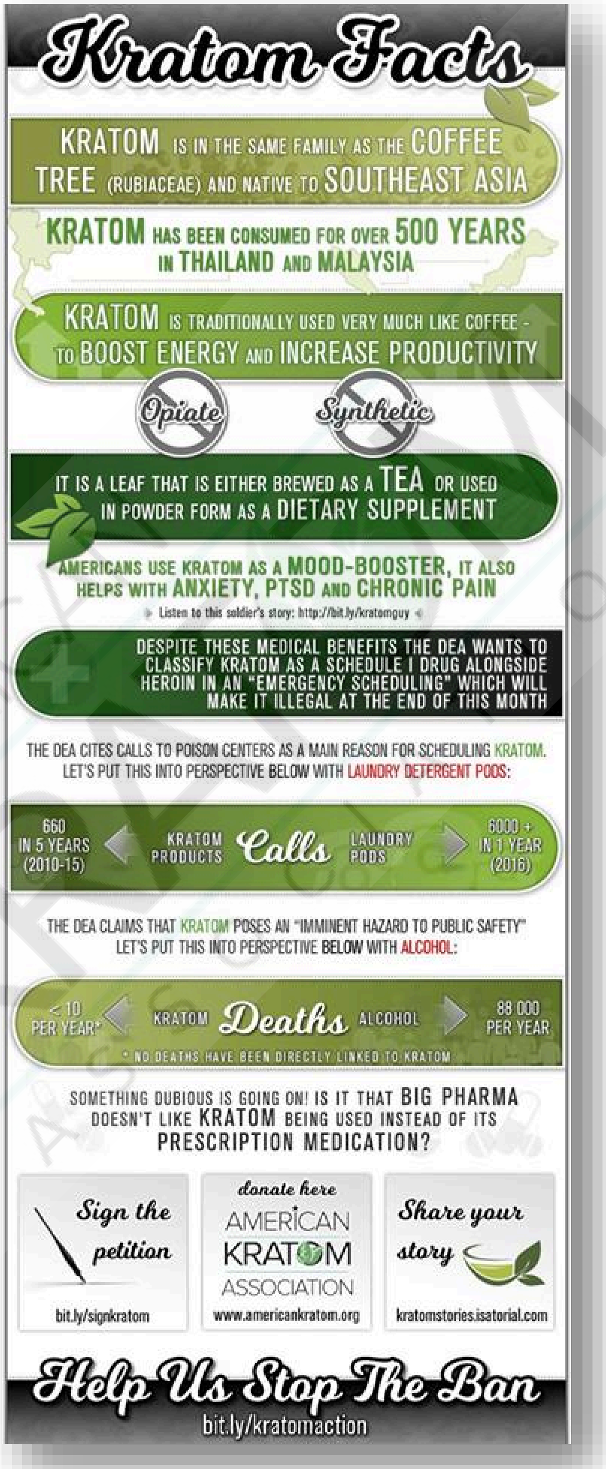
In southern Thailand, upwards of **70%** of the male population uses kratom on a DAILY BASIS in some areas.

REGULATION

There are very few RECORD available, showing negative **HEALTH** or **SOCIAL** consequences from kratom consumption.

When **CHEWED** or **BOILED** into a tea, kratom produces a mild, **CALMING** effect that most perceived as **HARMLESS.**

Many supporters believe criminalization of kratom is **UNFOUNDED** and based on economic control disinformation.



Kratom Facts

KRATOM IS IN THE SAME FAMILY AS THE COFFEE TREE (RUBIACEAE) AND NATIVE TO SOUTHEAST ASIA

KRATOM HAS BEEN CONSUMED FOR OVER 500 YEARS IN THAILAND AND MALAYSIA

KRATOM IS TRADITIONALLY USED VERY MUCH LIKE COFFEE - TO BOOST ENERGY AND INCREASE PRODUCTIVITY

Opiate
Synthetic

IT IS A LEAF THAT IS EITHER BREWED AS A TEA OR USED IN POWDER FORM AS A DIETARY SUPPLEMENT

AMERICANS USE KRATOM AS A MOOD-BOOSTER, IT ALSO HELPS WITH ANXIETY, PTSD AND CHRONIC PAIN

Listen to this soldier's story: http://bit.ly/kratomguy

DESPITE THESE MEDICAL BENEFITS THE DEA WANTS TO CLASSIFY KRATOM AS A SCHEDULE I DRUG ALONGSIDE HEROIN IN AN "EMERGENCY SCHEDULING" WHICH WILL MAKE IT ILLEGAL AT THE END OF THIS MONTH

THE DEA CITES CALLS TO POISON CENTERS AS A MAIN REASON FOR SCHEDULING KRATOM. LET'S PUT THIS INTO PERSPECTIVE BELOW WITH LAUNDRY DETERGENT PODS:

660 IN 5 YEARS (2010-15)	KRATOM PRODUCTS	Calls	LAUNDRY PODS	6000 + IN 1 YEAR (2016)

THE DEA CLAIMS THAT KRATOM POSES AN "IMMINENT HAZARD TO PUBLIC SAFETY" LET'S PUT THIS INTO PERSPECTIVE BELOW WITH ALCOHOL:

< 10 PER YEAR*	KRATOM	Deaths	ALCOHOL	88 000 PER YEAR

* NO DEATHS HAVE BEEN DIRECTLY LINKED TO KRATOM

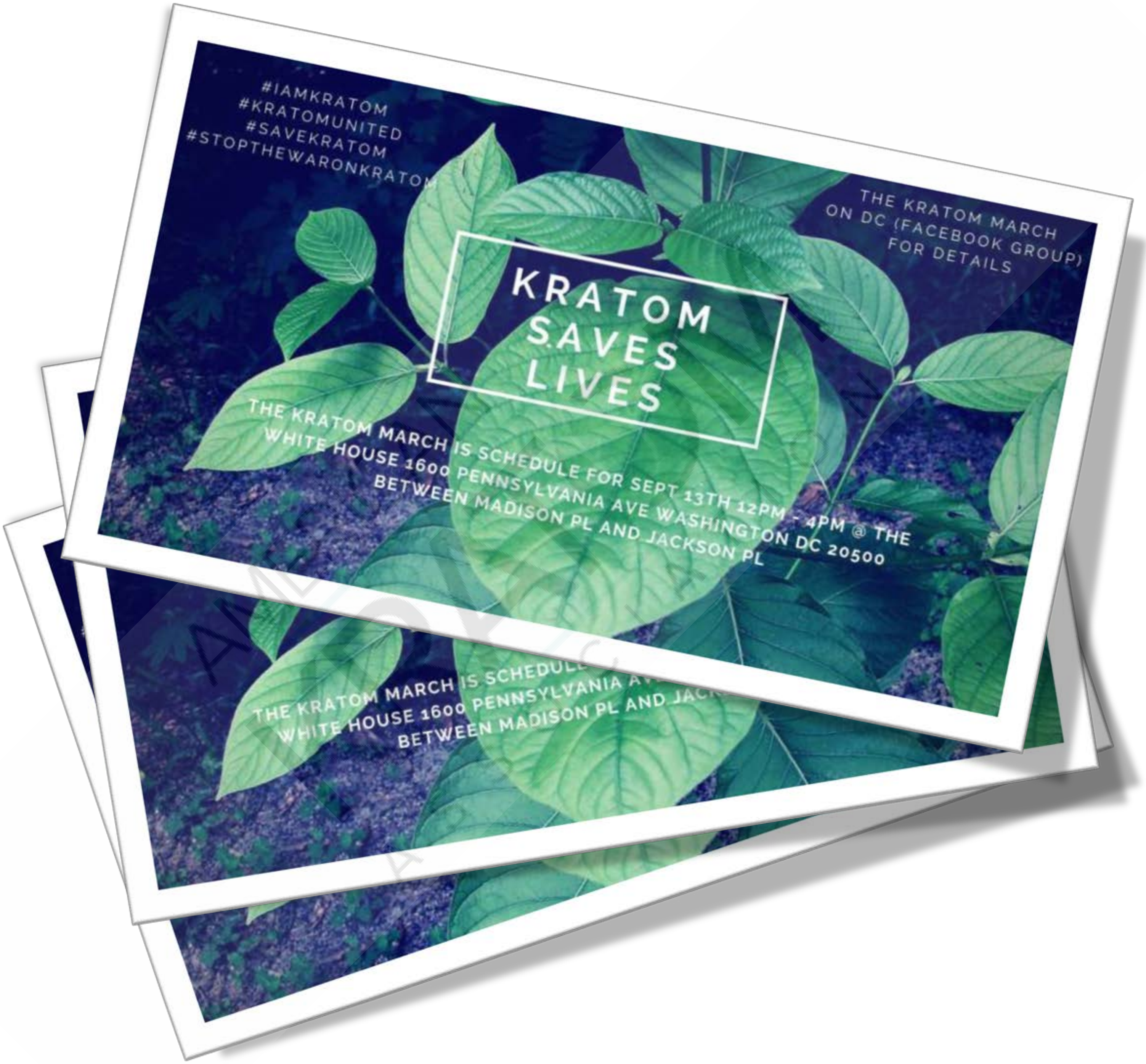
SOMETHING DUBIOUS IS GOING ON! IS IT THAT BIG PHARMA DOESN'T LIKE KRATOM BEING USED INSTEAD OF ITS PRESCRIPTION MEDICATION?

Sign the petition	donate here AMERICAN KRATOM ASSOCIATION	Share your story
bit.ly/signkratom	www.americankratom.org	kratomstories.isatorial.com

Help Us Stop The Ban

bit.ly/kratomaction

KRATOM
SAVES
LIVES
KRATOM
SAVES LIVES



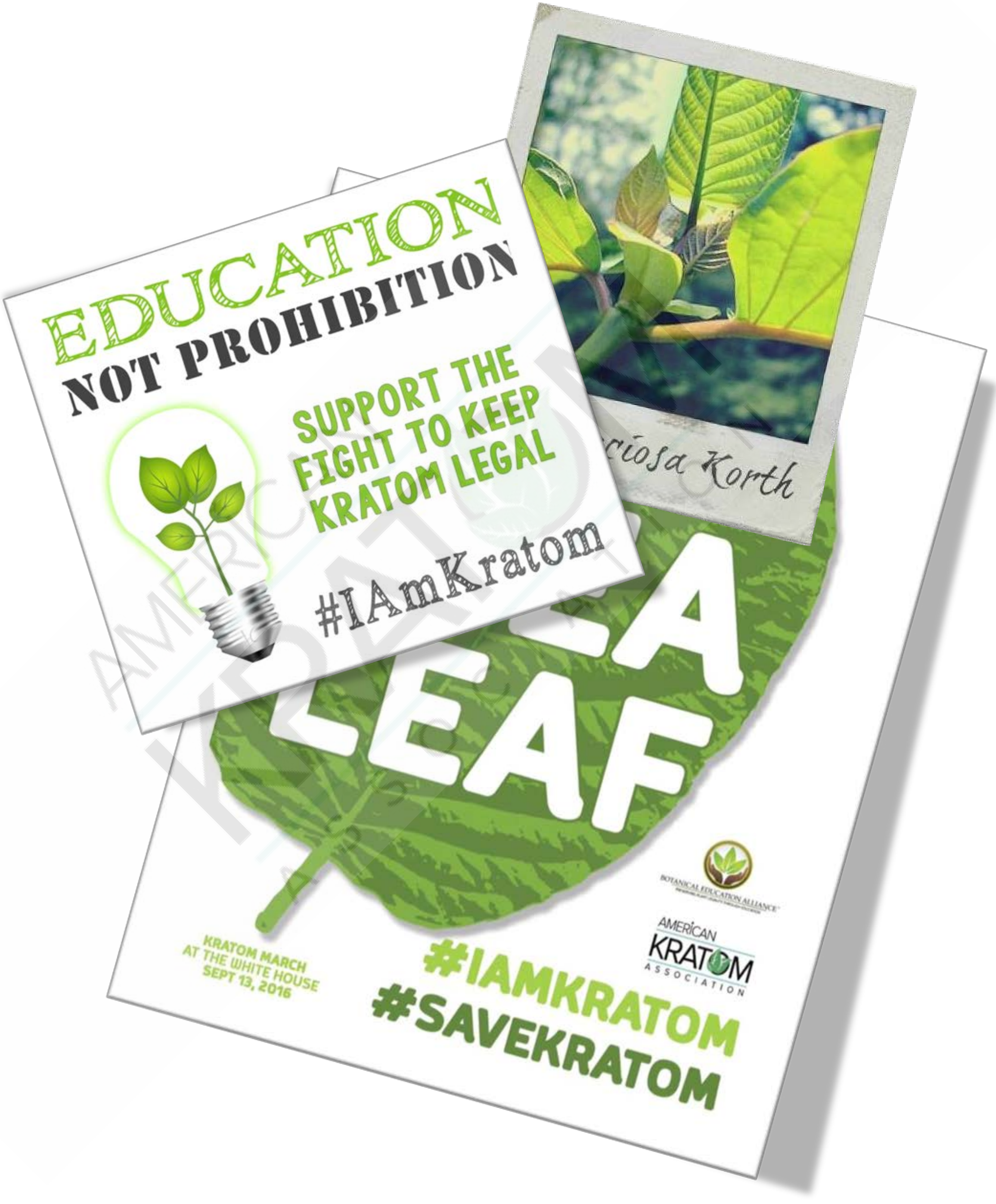
#IAMKRATOM
#KRATOMUNITED
#SAVEKRATOM
#STOPTHEWARONKRATOM

THE KRATOM MARCH ON DC (FACEBOOK GROUP) FOR DETAILS

KRATOM SAVES LIVES

THE KRATOM MARCH IS SCHEDULE FOR SEPT 13TH 12PM - 4PM @ THE WHITE HOUSE 1600 PENNSYLVANIA AVE WASHINGTON DC 20500 BETWEEN MADISON PL AND JACKSON PL

-KRATOM IS A 100%-
NATURAL
SOLUTION TO
AMERICA'S GROWING
ADDICTION PROBLEM


EDUCATION
NOT PROHIBITION
SUPPORT THE FIGHT TO KEEP KRATOM LEGAL
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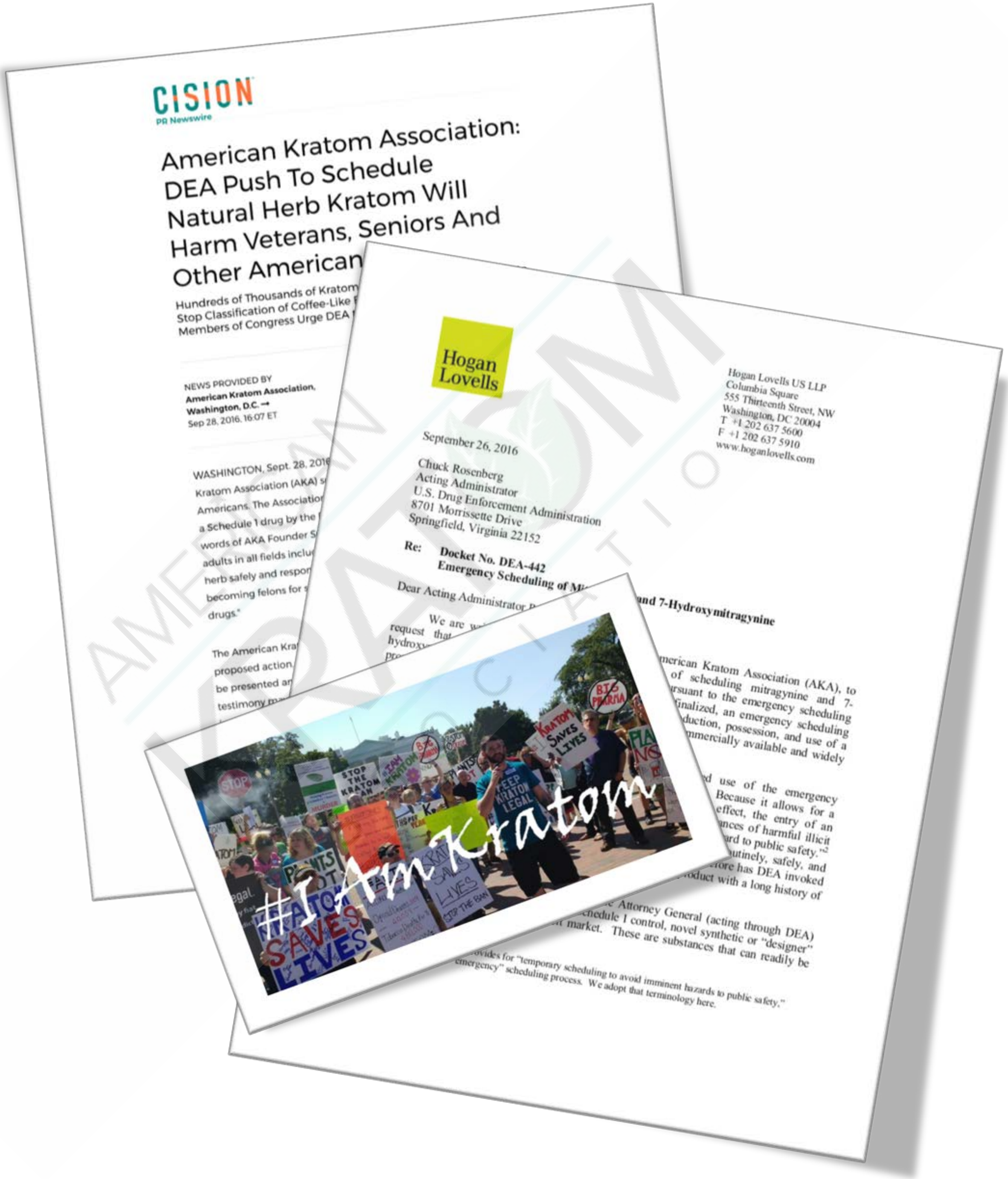
LEAF
KRATOM MARCH AT THE WHITE HOUSE SEPT 13, 2016
BOTANICAL EDUCATION ALLIANCE
AMERICAN KRATOM ASSOCIATION
#IAMKRATOM
#SAVEKRATOM



CISION
PR Newswire

American Kratom Association: DEA Push To Schedule Natural Herb Kratom Will Harm Veterans, Seniors And Other American

Hundreds of Thousands of Kratom
Stop Classification of Coffee-Like
Members of Congress Urge DEA

NEWS PROVIDED BY
American Kratom Association,
Washington, D.C. →
Sep 28, 2016, 16:07 ET

WASHINGTON, Sept. 28, 201
Kratom Association (AKA) s
Americans. The Associatio
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words of AKA Founder S
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The American Kra
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testimony m

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F +1 202 637 5910
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September 26, 2016

Chuck Rosenberg
Acting Administrator
U.S. Drug Enforcement Administration
8701 Morrissette Drive
Springfield, Virginia 22152

Re: Docket No. DEA-442
Emergency Scheduling of Mi and 7-Hydroxymitragynine

Dear Acting Administrator

We are w
request that
hydroxy
pro

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of scheduling mitragynine and 7-
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Because it allows for a
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utinely, safely, and
efore has DEA invoked
oduct with a long history of

e Attorney General (acting through DEA)
chedule I control, novel synthetic or "designer"
t market. These are substances that can readily be

ovides for "temporary scheduling to avoid imminent hazards to public safety,"
emergency" scheduling process. We adopt that terminology here.

AMERICAN KRATOM ASSOCIATION

American Kratom Association Introduces Two New Members to the Board of Directors

Newest Members of AKA Board Bring a Wide Range of Experience and Influence

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NEWS PROVIDED BY

American Kratom Association

July 05, 2017,

WASHINGTON, D.C.   July 6, 2017/

The American Kratom Association (AKA), the leading advocacy organization advancing and defending the coffee-like herb kratom, announced today the appointment of two new members, Michael Ostrolenk and Robert Kennedy III, to the Board of Directors. Both individuals are highly qualified and each bring a unique prospective that will be a tremendous asset to the organization.

Michael D. Ostrolenk is co-founder of the Liberty Coalition and the Medical Privacy Coalition and served as program manager for the Natural Health Research Institute. He also served as an analyst for the Association of American Physicians and Surgeons and Citizens for Health.

With these positions as well as many others, Michael has an extensive background and strong record of accomplishments in working with the heath industry and government policies, as he successfully convened initiatives to protect liberty, privacy and more.

Michael holds a MA from John F. Kennedy University and has a BA in Government.

Robert (Bobby) Kennedy III has been a long- time activist for Democracy, Environmentalism and Transparency in film and media. Bobby brings a unique perspective that will greatly enhance the ability of the AKA to communicate our message and develop strategies that will enable us to reach a larger audience of advocates.

Bobby has spent his career as a film maker, activist, and champion of protecting individual freedoms.

AKA Board Chair Herman said: “We are honored to add Michael and Bobby to the Board of Directors of the American Kratom Association. This addition continues to demonstrate our commitment to bringing in the right talent that will help us in our fight to keep kratom legal.”

The two new Board members join an already diverse and highly qualified Board of Directors.

As the leading advocacy group for kratom, the American Kratom Association is proud to be playing an instrumental role in helping to coordinate the broad-based national opposition to the Drug Enforcement Administration (DEA) attempt to effectively ban kratom:

- Released on March 16, 2017 an infographic debunking major myths about kratom, noting that the coffee-like herb: is not an opiate; attracted substantial support from doctors, veterans, scientists, and law enforcement officials when the DEA sought public comments last year; has not been proven to be the cause of a single death; and has no more potential for “substance use disorder” than caffeine.

- Submitted on March 1, 2017 a petition to U.S. President Donald J. Trump urging a halt to the DEA/Food and Drug Administration (FDA) push to criminalize kratom. Signed by 26,047 Americans, the online petition was launched by AKA on December 19, 2016.

- Coordinated with the American Coalition of Free Citizens to release a February 2, 2017 analysis showing that 99.1 percent of the 23,116 comments submitted to the DEA during a late 2016 public comment period (see below) opposed banning kratom. Of the 2416 commenters who listed a profession, nearly half (48 percent) were veterans, law enforcement officials, health care professionals, and scientists. This group of 1175 professionals came down strongly in favor of kratom and against a ban: 754 versus 9 … for a pro-kratom support level of 98.7 percent.

- Led the charge when the DEA opened a public comment period running through December 1, 2016. Of the more than 23,000 comments submitted before the deadline closed, the KratomComments.org Web site created by AKA was responsible for 16,379 comments – roughly 71 percent of the total comments received at Regulations.gov. (The AKA campaign Web site is now inactive.)

- Issued on November 30, 2016 a long-awaited analysis by Dr. Jack Henningfield, Ph.D., vice president of Research, Health Policy, and Abuse Liability at Pinney Associates, concluding that there is “insufficient evidence” for the U.S. Drug Enforcement Administration (DEA) to ban or otherwise restrict kratom under the Controlled Substances Act. According to the comprehensive Henningfield analysis, kratom’s potential for abuse and dependence is no greater than such widely used and unscheduled substances as “nutmeg, hops, St. John’s Wort, chamomile, guarana, and kola nut.”

- Conducted in November 2016 an online survey of 105 emergency room (ER)/trauma health care professionals that found zero reported cases of deaths related to kratom. The new poll of America's front-line medical professionals also uncovered precisely zero percent support among those surveyed for a DEA ban on the coffee-like herb kratom.

- Encouraged a set of two letters sent on October 1, 2016 by a politically diverse group of 11 Senators, including Sen. Orrin G. Hatch (R-UT), Sen. Ron Wyden (D-OR) and Sen. Cory Booker (D-NJ), calling on the DEA to halt the proposed scheduling and allow for a regular rulemaking process permitting the public, scientific experts, and Congress to provide input.

- Facilitated letters to the DEA and the Office of Management and Budget sent on September 2, 2016 by a bipartisan group of 51 U.S. House Members urging a halt to the DEA's push to ban kratom.

- Worked with the Pain News Network on a September 2016 survey of 6150 kratom users about their experience with the herb.

- Promoted a successful and widely publicized September 13, 2016 "March for Kratom" in September at the White House.

- Circulated a "We the People" petition targeting the White House that accumulated more than 142,000 signatures.

ABOUT AKA

The America Kratom Association, a consumer-based non-profit organization, is here to set the record straight, giving a voice to those suffering and protecting our rights to possess and consume kratom. AKA represents tens of thousands of Americans, each of whom has a unique story to tell about the virtues of kratom and its positive effects on their lives. www.americankratom.org

INQUIRIES: Pete Candland, (703) 608-4649 or pete.candland@americankratom.org

AMERICAN KRATOM ASSOCIATION

American Kratom Association Names New Board Chair and Board Member

NEWS PROVIDED BY

American Kratom Association

June 11, 2017

WASHINGTON, D.C June 11, 2017

The American Kratom Association (AKA), the leading advocacy organization advancing and defending the coffee-like herb kratom, announced today the appointment of a new board chair and a new member of its board. Both highly qualified individuals have decades of management and financial experience that will be leveraged to advance the important work of AKA.

The new chair of the Board of Directors is David Herman. Herman has experience in corporate management, finance, and nonprofit oversight, including extensive work in patient advocacy. After working 25 years as a Hotel Executive and a Mortgage/Investment Banker, he retired and began working in the nonprofit arena. Herman served for six years as the executive director and national spokesperson for the Seniors Coalition, a 501c (4) corporation. In that capacity, he testified before Congress and participated in extensive national and grassroots media campaigns.

More recently, Herman served as chair and CEO of a national patient advocacy group, the AMD Alliance International, a 501c (3) nonprofit corporation consisting of 70 member organizations in 25 countries. He served on the Patient Advisory Board for Genentech and was a member of the Novartis Power of Partnering group. Herman also worked on patient advocacy programs with Alcon Labs.

AKA Board Chair Herman said: “It is critically important that kratom and the five million Americans who consume it responsibly have a loud, clear and powerful voice speaking out for this beneficial herb. The American Kratom Association has always been at the forefront of this fight and we will remain there. It is our intention to move forward and cement our role as the leading and most effective advocacy organization for kratom and consumers of kratom.”

Joining Herman on the AKA board is new Board Member-at-Large Chris Bake, a resident of Las Vegas, NV. A skilled expert from the worlds of venture capital and marketing, Chris began his career working for CSB Marketing and Management Corporation, specializing in direct marketing activities in the Washington DC area.

After 16 years with CSB, Bake entered the nutritional arena through Nutrition for Life. While at Nutrition for Life, he became a strong advocate for non-traditional treatments and medicines, traveling around the world exploring different options for family members with serious illnesses. Bake believes deeply in the freedom of individuals to make their own decisions on their well-being.

For the last 15 years, Chris has built a successful organization as an independent venture capital consultant. Bake brings to the AKA board extensive experience in organizational fundraising, partnership development, and creative solutions.

The new steps to strengthen the board of directors of the American Kratom Association come after the recent decision by AKA Founder Susan Ash to transition her role to full-time spokesperson of the AKA.

As the leading advocacy group for kratom, the American Kratom Association is proud to be playing an instrumental role in helping to coordinate the broad-based national opposition to the Drug Enforcement Administration (DEA) attempt to effectively ban kratom:

- Released on March 16, 2017 an infographic debunking major myths about kratom, noting that the coffee-like herb: is not an opiate; attracted substantial support from doctors, veterans, scientists, and law enforcement officials when the DEA sought public comments last year; has not been proven to be the cause of a single death; and has no more potential for “substance use disorder” than caffeine.

- Submitted on March 1, 2017 a petition to U.S. President Donald J. Trump urging a halt to the DEA/Food and Drug Administration (FDA) push to criminalize kratom. Signed by 26,047 Americans, the online petition was launched by AKA on December 19, 2016.

- Coordinated with the American Coalition of Free Citizens to release a February 2, 2017 analysis showing that 99.1 percent of the 23,116 comments submitted to the DEA during a late 2016 public comment period (see below) opposed banning kratom. Of the 2416 commenters who listed a profession, nearly half (48 percent) were veterans, law enforcement officials, health care professionals, and scientists. This group of 1175 professionals came down strongly in favor of kratom and against a ban: 754 versus 9 … for a pro-kratom support level of 98.7 percent.

- Led the charge when the DEA opened a public comment period running through December 1, 2016. Of the more than 23,000 comments submitted before the deadline closed, the KratomComments.org Web site created by AKA was responsible for 16,379 comments – roughly 71 percent of the total comments received at Regulations.gov. (The AKA campaign Web site is now inactive.)

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- Encouraged a set of two letters sent on October 1, 2016 by a politically diverse group of 11 Senators, including Sen. Orrin G. Hatch (R-UT), Sen. Ron Wyden (D-OR) and Sen. Cory Booker (D-NJ), calling on the DEA to halt the proposed scheduling and allow for a regular rulemaking process permitting the public, scientific experts, and Congress to provide input.

- Facilitated letters to the DEA and the Office of Management and Budget sent on September 2, 2016 by a bipartisan group of 51 U.S. House Members urging a halt to the DEA’s push to ban kratom.

- Worked with the Pain News Network on a September 2016 survey of 6150 kratom users about their experience with the herb.

- Promoted a successful and widely publicized September 13, 2016 “March for Kratom” in September at the White House.

- Circulated a “We the People” petition targeting the White House that accumulated more than 142,000 signatures.

ABOUT AKA

The America Kratom Association, a consumer-based non-profit organization, is here to set the record straight, giving a voice to those suffering and protecting our rights to possess and consume kratom. AKA represents tens of thousands of Americans, each of whom has a unique story to tell about the virtues of kratom and its positive effects on their lives. www.americankratom.org

INQUIRIES: Pete Candland, (703) 608-4649 or pete.candland@americankratom.org

AMERICAN KRATOM ASSOCIATION

STOP THE IMPORTATION AND TRAFFICKING OF SYNTHETIC ANALOGUES ACT OF 2017 (SITSA Act)

PROVIDED BY

American Kratom Association

June 11, 2017

WASHINGTON, D.C June 11, 2017

Senator Chuck Grassley (R-IA) and Senator Diane Feinstein (D-CA) filed S. 1327, the SISTA Act, that attempts to respond to the threat posed by “analogues” of already-controlled substances that pose a danger through the street drug and opioid epidemic. A companion bill, H.R. 2581, has also been filed by Representative John Katko (R-NY).

It is clear that the Department of Justice (DOJ) and the Drug Enforcement Administration (DEA) are seeking additional powers to address how controlled substance analogues are to be regulated to address the problem with synthetic street drugs that are killing users. But this expansion of powers being granted to DOJ and DEA poses a significant threat to kratom, and potentially other botanical and herbal supplements, if these agencies decide to use the new powers that would be granted by this legislation.

Current Landscape: The August 31, 2016 Federal Register Notice by the DEA attempted to use the emergency scheduling authority to interdict dangerous and often lethal street drugs to ban consumer access to kratom and kratom products. On October 13, 2016, the DEA was forced to withdraw its proposed scheduling order in the face of an outcry from kratom supporters, including a bi-partisan group of U.S. House and Senate members.

That has made kratom an issue of substantial and embarrassing controversy within the DEA. There were more than 80 previous Emergency Scheduling Notices that were filed and successfully implemented by the DEA before the unprecedented withdrawal of their “Emergency Scheduling Notice” for kratom in October 2016. Based on reports with various staffers on the Hill, the DEA’s “scorecard” on the kratom withdrawal was both an embarrassment and, in their view, remains as “unfinished business.”

Issues of Concern with SITSA: In order to properly understand the effect of the proposed legislative change to the Control Substances Act, it is important to look at the proposed expansion of powers given to the Attorney General under the proposed "Schedule A" designation.

What constitutes a "controlled substance analogue" is the critical question in the context of this proposed legislation. The term "analogue" is actually a very vague term that has a variety of meanings that are all dependent upon the context in which the word is used.

In pharmacology, the term "analogue" refers to one of two specific concepts:

1. Functional analogue: A chemical compound with similar properties to another;
2. Structural analogue: A chemical compound with a slightly altered chemical structure compared to another.

Whether or not a compound is an "analogue" is independent of whether it is natural or not. In that context, prosecutors can argue that natural mitragynine is a morphine analogue because it produces similar effects.

There have been numerous studies on kratom and its alkaloids that can and likely will be used by government attorneys to argue that kratom poses a threat to public safety, and those alkaloids are, in their view, analogues of controlled substances. The issue will not be whether the conclusions of such studies are accurate or not, it will only be that the government has a credible basis to add kratom to the new "Schedule A."

As an example, in a study presented by Dr. Irna Elina Ridzwan at a 2015 workshop for the International Islamic University Malaysia's Repository System, reported as follows:

"Like morphine, mitragynine mainly acts at mu-opioid receptor which is the main target to treat opioid dependency."

In a report published in the Journal of American Chemical Society on May 18, 2016, Dr. Andrew Kruegel of Columbia University and several colleagues drew the following conclusion:

"These results show that mitragynine and the oxidized analogue 7-hydroxymitragynine, are partial agonists of the human mu-opioid receptor and competitive antagonists at the kappa- and delta-opioid receptors."

Another research report, "From Kratom to mitragynine and its derivatives: Physiological and behavioral effects related to use, abuse, and addiction," done by a group of researchers published in the Neuroscience & Biobehavioral Reviews (Volume 37, Issue 2, February 2013), concluded as follows:

"Mitragynine and its derivatives actions in the central nervous system involve μ-opioid receptors, neuronal Ca2+ channels and descending monoaminergic projections. Altogether, available data currently suggest both, a therapeutic as well as an abuse potential."

A report published in The Journal of the American Osteopathic Association, December 2012, "Pharmacology of Kratom: An Emerging Botanical Agent with Stimulant, Analgesic and Opioid-Like Effects," concluded as follows:

"Recent studies have shown that kratom contains a variety of active compounds that produce major pharmacologic effects at opioid and other receptors. Kratom and kratom-derived drugs may potentially be used for the management of pain, opioid withdrawal symptoms, and other clinical problems."

Finally, the conclusions of the European Monitoring Centre for Drugs and Drug Addiction provide a damning assessment of kratom's opioid-like effects:

"In general, the effects of kratom in humans are dose-dependent: small doses produce 'cocaine-like' stimulation while larger dosages cause 'morphine-like' sedative-narcotic effects."

These are just a few examples of studies that draw a close correlation between the alkaloids in kratom and their opioid counterparts that are scheduled as controlled substances. These studies, and many like them, will provide ample argumentation for government regulators to argue that kratom should be construed as an analogue of opioids on the Controlled Substances Schedule I. It is a well-established precedent in the courts that judges will yield to the scientists when it comes to complex pharmacologic effects of substances.

Some states have banned kratom on the basis that it is an analogue for controlled substances, and their underlying reasoning has not been questioned to date.

The proposed SITSA legislation in Section 2, Establishment of Schedule A, outlines the criteria for the inclusion of any substance that (1) has a chemical structure that is substantially similar to the chemical structure of a controlled substance in schedule I, II, III, IV, or V; and (2) an actual or predicted stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than that of a controlled substance already scheduled.

The Act goes on to create even more potential havoc for kratom:

"For the purpose of this paragraph, the predicted stimulant, depressant, or hallucinogenic effect on the central nervous system may be based on (i) the chemical structure, structure activity relationships, binding receptor assays, or other relevant scientific information about the substance; (ii)(I) the current or relative potential for abuse of the substance; and (II) the clandestine importation manufacture, or distribution, or diversion from legitimate channels, of the substance; or (iii) the capacity of the substance to cause a state of dependence, including physical or physiological dependence that is similar to or greater than that of a controlled substance" that is already scheduled.

In DEA's justification for the August 31, 2016 "Temporary Placement of Mytragynine and 7-Hydroxymitragynine Into Schedule I", it is clear in its intent to define kratom as an opioid that should be controlled, including the following stated evidence:

- Kratom is abused for its ability to produce opioid-like effects.
- Attempted importations of kratom are routinely miss-declared and falsely labeled.
- Considerations of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution.
- Available information indicates that these opioid substances, constituents of the plant kratom, have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.
- Kratom, which contains the main active alkaloids, mytragynine and 7-hydroxymitragynine, has a long history of use in Southeast Asia as an opium substitute.
- In recent years, the presence of the psychoactive plant kratom has increased dramatically in the recreational market in the United States due to its opioid-like effects.
- In the United States, kratom is misused to self-treat chronic pain and opioid withdrawal symptoms, with users reporting its effects to be comparable to prescription opioids.
- Kratom is abused for its ability to produce opioid-like effects.
- Users have also reported dose-dependent psychoactive effects to include euphoria, simultaneous stimulation and relaxation, analgesia, vivid dreams, and sedation (at higher doses).
- The FDA stated that kratom products "pose a risk to the public health and have the potential for abuse", and the seizure of certain kratom products was necessary "to safeguard the public from a dangerous product".
- These substances produce opioid-like effects, making their abuse a serious public health concern.
- Reports of hepatotoxicity, psychosis, seizure, weight loss, insomnia, tachycardia, vomiting, poor concentration, hallucinations, and death associated with kratom use have been documented.

In that Notice, the DEA outlined a very specific case against kratom because it is, in their judgment, associated directly with substances that are already scheduled. The only protection the kratom community has been able to utilize to this point under the current law is the fact that there are very specific statutory limits on the procedural and evidentiary requirements set forth by the DEA in its Federal Register Notice, and under those requirements the DEA failed to meet their evidentiary burden for emergency scheduling.

The SITSA Act grants broad new powers to the Attorney General that will be predicated upon a much lower standard of evidence to schedule kratom and potentially other botanicals in the newly created Schedule A. Based on the publicly declared position of the DEA, it would not be unreasonable to expect that kratom would be added to Schedule A if this legislation were passed. Given that there is no judicial review permitted for such scheduling in the proposed law, consumers would be denied access to kratom and would be stripped of their freedoms to make their own personal health and well-being decisions.

The merit of most public policy decisions by the Congress is evaluated on the “risk-matrix” of what could happen if legislation were to pass. Based on the available evidence, the proposed legislation needs to be amended, at a minimum, to provide an exemption for natural botanical products (including kratom), or kratom advocates must work to defeat the bill completely.

Ultimately, if the AKA defers on any attempt to amend this legislation, it requires a “trust” in the DEA and the FDA to act responsibly with respect to kratom. That approach puts every kratom user, and the products provided by the kratom industry, at substantial risk.

PR Newswire

Pinney Associates Scientific Abuse Potential Assessment of Kratom Finds Evidence of Public Health Benefit and Little Harm

The DEA Withdraws Proposed Emergency Scheduling and Prohibition on Kratom, Allowing Consumers to Continue Lawful Use, Potential FDA Oversight, and Expanded Research

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NEWS PROVIDED BY

Pinney Associates→

Jan 18, 2017, 10:26 ET

BETHESDA, Md., Jan. 18, 2017 /PRNewswire/ Kratom leaves, from a South East Asian tree in the coffee family, are often used to prepare tea-like beverages and commercially manufactured products which are consumed by several million Americans annually to increase alertness, enhance wellbeing and occupational performance, and as a natural remedy for minor aches and pains. Pinney Associates' review of the scientific evidence regarding kratom's effects is intended to assist FDA and DEA in determining the most appropriate regulatory approach within FDA authority to permit appropriate use, minimize unintended effects, encourage research, and contribute to the enhancement of public health.

DEA had proposed placing kratom in Schedule I (which includes drugs such as heroin and LSD), the most restrictive category of the Controlled Substances Act. In practical terms, this would have banned the sale of kratom and posed a major roadblock to research. The American Kratom Association petitioned the DEA to withdraw its proposal. Pinney Associates' was then contracted to review the available information about kratom and develop an "8-factor analysis", the legal framework used to assess the abuse potential of substances, about kratom for submission to the FDA, DEA, and National Institute on Drug Abuse to inform the deliberations regarding regulation of kratom. See more about this in press coverage by Wired, Forbes, and the Washington Post.

One of the authors of the kratom 8-factor analysis was Dr. Jack Henningfield, Vice President of Research, Health Policy and Abuse Liability, at Pinney Associates, and Adjunct Professor of Behavioral Biology, Johns Hopkins University School of Medicine. Dr. Henningfield commented, "It's important to understand that although kratom has some mild effects similar to opioids, its chemical make-up is different, and it appears overall much safer, with apparently relatively small effects on respiration. In fact, kratom's analgesic effects and impact on energy, combined with its favorable safety profile supports continued access by consumers to appropriately regulated kratom products while research on its uses continues." Furthermore, he said "surveys suggest that kratom products are used by many former opioid users as a natural remedy to help them abstain from opioids."

Dr. Henningfield concluded, "Our work on kratom is an example of how we help regulators and industry make scientifically informed decisions about the risks and benefits of pharmaceuticals and nutritional supplements. This is a key facet of the work we produce at the intersection of science and public health policy." The kratom abuse potential assessment is an example of the comprehensive abuse potential assessments and CSA 8-factor assessments that Pinney Associates scientists develop for pharmaceutical companies to submit to the FDA in support of CNS-acting products including opioids, ADHD stimulants, anti-epileptics, and sedative sleep aids.

ABOUT PINNEY ASSOCIATES

Pinney Associates is a pharmaceutical and consumer healthcare consulting company that helps clients to reduce their regulatory risk and enhance the commercial value of their life sciences products. Pinney Associates consults with pharmaceutical companies that market a wide variety of prescription and over-the-counter medications. Pinney Associates' experts have extensive expertise in abuse-deterrent drug formulation evaluation, abuse potential assessment, as well as pharmaceutical risk management, Rx-to OTC switch, and tobacco harm reduction.

For more information about Pinney Associates, please contact us at +1.301.718.8440 or info@pinneyassociates.com, or learn more about our work at www.pinneyassociates.com.

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CISION
PR Newswire

More Than 26,000 Petition President Trump To Stop DEA's War On Coffee-Like Herb Kratom

Weeks After 99% of 23,000+ Comments to DEA Opposed Kratom Ban, Petition Urges End to "Regulatory Overkill" On A Botanical With No More Abuse Potential Than Nutmeg

NEWS PROVIDED BY
American Kratom Association, Washington, DC →
Mar 01, 2017, 13:30 ET

WASHINGTON, March 1, 2017 /PRNewswire-USNewswire/ -- A total of 26,047 Americans signed a petition to Donald Trump urging the new president to halt the Drug Enforcement Administration (DEA)/Food and Drug Administration (FDA) push to criminalize kratom. The online petition was launched by the American Kratom Association (AKA) on December 19, 2016.

In late November, AKA released a report by one of the world's leading addiction experts concluding that kratom has no more potential for abuse and dependence than nutmeg and St. John's Wort.

The petition and list of signers is being presented to the White House today by the American Kratom Association.

American Kratom Association Director Susan Ash said: **"We are sending a strong message from the kratom community to the new White House that the attack on kratom producers and consumers must end. There is no room in an Administration committed to limited government and allowing responsible adults to live free lives for the DEA's regulatory overkill response to kratom. Coming as this does just weeks after the DEA comment period attracted 23,000 some comments that were 99 percent opposed to a kratom ban, the message for President Trump could not be clearer."**

The petition to the new President reads in part as follows:

"Your promise to end excessive government regulations and restore the limited role of government in the lives of Americans is the reason that we are appealing to you today.

The three-five million Americans who choose to use the natural herb kratom to maintain their well-being desperately need your help. We are concerned that the Drug Enforcement Administration may soon choose to curb access to this herb … If the DEA has not acted by January 21st, we ask that you put an end to regulatory proceedings targeting kratom.

The DEA and the U.S. Food and Drug Administration have openly declared war on kratom consumers, and these agencies are blatantly abusing their powers to criminalize both those who produce and sell kratom products, and those who purchase and consume them. These federal regulators are doing all they can to deny American consumers their freedom to make individual choices on the safe products they want to use to maintain their health and well-being.

Despite credible evidence proving kratom is no more addictive than a cup of coffee, and its use presents no threat to the public health, the DEA and the FDA are continuing their efforts to classify kratom as a dangerous drug – with the same classification as heroin or cocaine.

Who are we?

We are veterans … and lawyers … and factory workers … and school teachers … and health care professionals. We are mothers and fathers … and grandparents and senior citizens.

We are the real face of America. Our choice to consume kratom does not make us 'drug abusers' any more than drinking a cup of coffee would …"

The American Kratom Association is proud to be playing an instrumental role in helping to coordinate the broad-based national opposition to the DEA's attempt to effectively ban kratom. In addition to creating the Petition Trump For Kratom campaign, AKA also:

- Coordinated with the American Coalition of Free Citizens to release a February 2, 2017 analysis showing that 99.1 percent of the 23,116 comments submitted to the DEA during a late 2016 public comment period (see below) opposed banning kratom. Of the 2,416 commenters who listed a profession, nearly half (48 percent) were veterans, law enforcement officials, health care professionals, and scientists. This group of 1,175 professionals came down strongly in favor of kratom and against a ban: 754 versus 9 … for a pro-kratom support level of 98.7 percent.
- Led the charge when the DEA opened a public comment period running through December 1, 2016. Of the more than 23,000 comments submitted before the deadline closed, the KratomComments.org Web site created by AKA was responsible for 16,379 comments – roughly 71 percent of total comments received at Regulations.gov. (The AKA campaign Web site is now inactive.)
- Issued on November 30, 2016 a long-awaited analysis by Dr. Jack Henningfield, Ph.D., vice president of Research, Health Policy, and Abuse Liability at PinneyAssociates, concluding that there is "insufficient evidence" for the U.S. Drug Enforcement Administration (DEA) to ban or otherwise restrict kratom under the Controlled Substances Act. According to the comprehensive Henningfield analysis, kratom's potential for abuse and dependence is no greater than such widely used and unscheduled substances as "nutmeg, hops, St. John's Wort, chamomile, guarana, and kola nut."
- Conducted in November 2016 an online survey of 105 emergency room (ER)/trauma health care professionals that found zero reported cases of deaths related to kratom. The new poll of America's front-line medical professionals also uncovered precisely zero percent support among those surveyed for a DEA ban on the coffee-like herb kratom.
- Encouraged a set of two letters sent on October 1, 2016 by a politically diverse group of 11 Senators, including Sen. Orrin G. Hatch (R-UT), Sen. Ron Wyden (D-OR) and Sen. Cory Booker (D-NJ), calling on the DEA to halt the proposed scheduling and allow for a regular rulemaking process permitting the public, scientific experts, and Congress to provide input.

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- Circulated a "We The People" petition targeting the White House that accumulated more than 142,000 signatures.

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SOURCE American Kratom Association, Washington, DC

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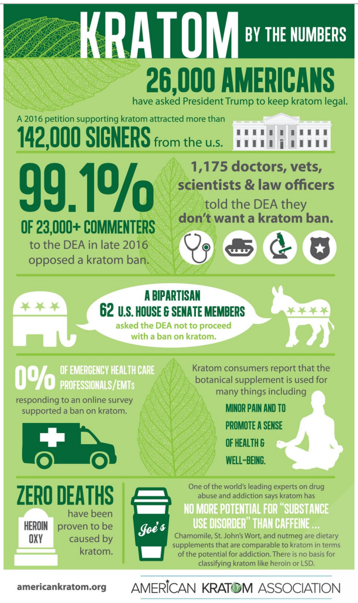
CISION
PR Newswire

American Kratom Association Urges Local Authorities To Stop Unscientific Attacks On Kratom

Action Spurred by Spate of Unfounded Warnings in GA, VA, AL, CO and UT; "Reefer Madness"-Style Fear Campaign Linked to 2016 DEA Briefings, New Infographic Sets the Record Straight.

NEWS PROVIDED BY
American Kratom Association, Washington, DC →
Mar 16, 2017, 11:00 ET

WASHINGTON, March 16, 2017 /PRNewswire-USNewswire/ -- Even though the case for banning or scheduling kratom has been debunked, there continue to be a number of unwarranted warnings about the coffee-like botanical coming from city, county and state agencies across the United States. In calling for a halt to these unscientific attacks on kratom, the American Kratom Association today issued a new fact-versus-fiction infographic at http://tinyurl.com/gvwbsk5.



KRATOM BY THE NUMBERS

26,000 AMERICANS have asked President Trump to keep kratom legal.

A 2016 petition supporting kratom attracted more than 142,000 SIGNERS from the u.s.

99.1% OF 23,000+ COMMENTERS to the DEA in late 2016 opposed a kratom ban.

1,175 doctors, vets, scientists & law officers told the DEA they don't want a kratom ban.

A BIPARTISAN 62 U.S. HOUSE & SENATE MEMBERS asked the DEA not to proceed with a ban on kratom.

0% OF EMERGENCY HEALTH CARE PROFESSIONALS/EMTs responding to an online survey supported a ban on kratom.

Kratom consumers report that the botanical supplement is used for many things including MINOR PAIN AND TO PROMOTE A SENSE OF HEALTH & WELL-BEING.

ZERO DEATHS have been proven to be caused by kratom.

One of the world's leading experts on drug abuse and addiction says kratom has NO MORE POTENTIAL FOR "SUBSTANCE USE DISORDER" THAN CAFFEINE ... Chamomile, St. John's Wort, and nutmeg are dietary supplements that are comparable to kratom in terms of the potential for addiction. There is no basis for classifying kratom like heroin or LSD.

The American Kratom Association issued this fact-versus-fiction infographic debunking a number of unscientific attacks on the coffee-like botanical kratom, which is no more addictive than nutmeg.

The local and state warnings appear to be an outgrowth of the one or more briefings conducted last fall by the Drug Enforcement Administration (DEA) with police and health officials across the United States. The AKA has learned of the DEA briefing or briefings, which were held before the point in time when the federal agency put on hold its plan to schedule kratom as an illegal drug.

To date, AKA has uncovered unfounded anti-kratom warnings issued by the Floyd County Police Department in Georgia, the Winchester (VA) Police Department, the Oxford (AL) Police Department, the City of Denver, and the Utah Poison Control Center. Though the City of Denver backed off its initial kratom ban, it has not withdrawn its related public health warning. The Utah agency has gone so far as to label kratom incorrectly as a "toxin."

To address any remaining pockets of anti-kratom hysteria, the new AKA fact-versus-fiction infographic seeks to set the record straight by focusing on such key facts as the following:

- 1,175 doctors, veterans, scientists and law enforcement officers told the DEA they don't want a kratom ban.

- 0 percent of emergency health care professionals (including nurses and surgeons) responding to an online survey favored a ban on kratom.

- Zero deaths have been proven to be caused by kratom.

- One of the world's leading experts on drug abuse and addiction says kratom has no more potential for "substance use disorder" than caffeine. Chamomile, St John's Wort, and nutmeg are dietary supplements that are comparable to kratom in terms of their potential for addiction.

- Kratom consumers report that the botanical supplement is consumed for many things, including the management of minor pain and to promote a sense of health and well-being.

American Kratom Association Director Susan Ash said: **"We are calling for state and local officials to recognize that the DEA backed away from its move to ban kratom after being faced with substantial public opposition and expert testimony that such a scheduling move is unjustified. As such, it is time to end the 'Reefer Madness'-style attacks on this coffee-like botanical that is used responsibly by myself and three-five million other Americans. It's not as though these officials don't have real problems to deal with today. We have a real opioid epidemic unfolding in this country. Federal, state, and local officials would be much better off focusing on that bona fide public health crisis, instead of trying to stoke unfounded fears about an imaginary 'kratom problem'."**

The American Kratom Association is proud to be playing an instrumental role in helping to coordinate the broad-based national opposition to the DEA's attempt to effectively ban kratom:

- Submitted on March 1, 2017 a petition to U.S. President Donald J. Trump urging a halt to the DEA/Food and Drug Administration (FDA) push to criminalize kratom. Signed by 26,047 Americans, the online petition was launched by AKA on December 19, 2016.

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- Issued on November 30, 2016 a long-awaited analysis by Dr. Jack Henningfield, Ph.D., vice president of Research, Health Policy, and Abuse Liability at PinneyAssociates, concluding that there is "insufficient evidence" for the U.S. Drug Enforcement Administration (DEA) to ban or otherwise restrict kratom under the Controlled Substances Act. According to the comprehensive Henningfield analysis, kratom's potential for abuse and dependence is no greater than such widely used and unscheduled substances as "nutmeg, hops, St. John's Wort, chamomile, guarana, and kola nut."

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- Encouraged a set of two letters sent on October 1, 2016 by a politically diverse group of 11 Senators, including Sen. Orrin G. Hatch (R-UT), Sen. Ron Wyden (D-OR) and Sen. Cory Booker (D-NJ), calling on the DEA to halt the proposed scheduling and allow for a regular rulemaking process permitting the public, scientific experts, and Congress to provide input.

- Facilitated letters to the DEA and the Office of Management and Budget sent on September 2, 2016 by a bipartisan group of 51 U.S. House Members urging a halt to the DEA's push to ban kratom.

- Worked with the Pain News Network on a September 2016 survey of 6150 kratom users about their experience with the herb.

- Promoted a successful and widely publicized September 13, 2016 "March for Kratom" in September at the White House.

- Circulated a "We The People" petition targeting the White House that accumulated more than 142,000 signatures.

ABOUT AKA

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SOURCE American Kratom Association, Washington, DC

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CISION
PR Newswire

Review Of DEA Kratom Public Comments Shows Strong Support Among Vets, Doctors, Cops And Seniors For Coffee-Like Herb

99.1% of 23,116 Comment Filers Supported Kratom and Opposed DEA Ban; Vets Seen as 18% of Filers Mentioning Profession, While Seniors Accounted for 21% Where Age Mentioned.

NEWS PROVIDED BY
American Kratom Association and American Coalition of Free Citizens, Washington, DC →
Feb 02, 2017, 15:52 ET

WASHINGTON, Feb. 2, 2017 /PRNewswire-USNewswire/ -- When the U.S. Drug Enforcement Agency (DEA) asked for public comments late last year about its plan to impose what amounted to a ban on the coffee-like herb kratom, they may not have been prepared for both the volume of comments (23,116) and the overwhelming opposition to a ban (99.1 percent). A new analysis by the American Kratom Association (AKA) and American Coalition of Free Citizens (ACFC) reviewed every one of the comments submitted to the DEA prior to the conclusion of its public comment period on December 1, 2016.

The AKA/ACFC found several things that the DEA most likely was not expecting to see:

- ***Overview of key groups.*** Among those listing a profession, nearly half (48 percent) were veterans, law enforcement officials, health care professionals, and scientists. (This reflected a total of 1175 out of 2416 comments with profession-related information.) These groups came down strong in favor of kratom and against a ban 754 versus 9 … for a pro-kratom support level of 98.7 percent.
- ***Veterans.*** Those who served in the military were a large contingent among those mentioning their profession. The 449 self-identified veterans accounted for 448 comments, or 18 percent of the 2416 indicating a professional work/background. Veterans supported kratom by a margin of 448 to 1, or 99.8 percent.
- ***Health care professionals.*** The 576 self-identified medical professionals in the survey also came down strongly in support of kratom. These current and retired doctors, nurses, and other medical professionals supported kratom by a margin of 569 to 7, or 98.8 percent.
- ***Older Americans.*** On age, a total of 3811 comment filers indicate how old they are. In this group, 806 (21 percent) were 55 or older. Older American supported kratom by a margin of 805 to 1, or 99.9 percent.

Susan Ash, director, American Kratom Association and Jason Jeffers, president, American Coalition of Free Citizens said: **"The face of kratom consumers is the face of America today. Our groups partnered-up to examine all of the public comments to DEA on the kratom ban because we were curious about who was responding and what they had to say. What we found is a kratom community of responsible consumers who look just like your family and the people who live next door. The results speak for themselves: 99 percent of those who comment, do not want the federal government to police the natural herb called kratom."**

Katie Lair, research and communications director, American Coalition of Free Citizens, said: **"The most curious thing about the public comments is that there were so few responses actually supporting the DEA. Only 113 people out of 23,116 commented in support of the DEA proposal to ban kratom. When you have so much anti-kratom propaganda circulating at**

the state level and misleading talk of a public health crisis, one would expect more public comments in support of what the DEA is trying to do. To have just 113 people nationwide support the DEA is remarkable for a campaign like this to determine whether something should be banned for the entire nation. The topline finding is obvious: There is no public appetite for banning kratom and continued fierce opposition can be expected by anyone who cares to do so."

For this research, medical professional was defined as "medical doctors, registered nurses, psychiatrists, speech therapists and EMTs and trained first responders."

The American Kratom Association led the charge when the DEA opened a public comment period running through December 1, 2016. Of the more than 23,000 comments submitted before the deadline closed, the KratomComments.org Web site created by AKA was responsible for 16,379 comments – roughly 71 percent of total comments received at Regulations.gov. (The campaign Web site is now inactive.)

The findings released today by the two groups are consisted with data released by AKA in a November 2016 online survey of 105 emergency room (ER)/trauma health care professionals that found zero reported cases of deaths related to kratom. The new poll of America's front-line medical professionals also uncovered precisely zero percent support among those surveyed for a DEA ban on the coffee-like herb kratom.

A major analysis by Dr. Jack Henningfield, Ph.D., vice president of Research, Health Policy, and Abuse Liability at PinneyAssociates, for the American Kratom Association found that there is "insufficient evidence" for the DEA to ban or otherwise restrict the coffee-like herb kratom under the Controlled Substances Act. According to the comprehensive Henningfield report, kratom has little potential for abuse and dependence – as low or lower than such widely used and unscheduled substances as "nutmeg, hops, St. John's Wort, chamomile, guarana, and kola nut."

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ABOUT ACFC

American Coalition of Free Citizens (ACFC), a non-partisan organization with members in every state, was founded in 2016 after a statewide ban on the natural herb kratom took effect in Alabama. Our core mission is to defend the rights of people to access and choose safe and natural ethnobotanical/herbal alternatives to prescription drugs. More broadly, ACFC defends the freedoms, rights and privileges granted to all Americans by the U.S. Constitution. As a result of the war on kratom initiated by both the federal government and state governments across the country, our group is committed to defending kratom and keeping it legal. The ACFC website is currently under construction set to launch in late winter 2017. Our Facebook group page can be found online at: https://www.facebook.com/groups/1301010013260823/ and our like page here: https://www.facebook.com/americfc/.

For queries about membership, volunteering or just general information, please contact our communications department at: americfc2017@gmail.com.

SOURCE American Kratom Association and American Coalition of Free Citizens, Washington, DC

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http://www.americankratom.org

CISION
PR Newswire

PinneyAssociates' Scientific Abuse Potential Assessment of Kratom Finds Evidence of Public Health Benefit and Little Harm

The DEA Withdraws Proposed Emergency Scheduling and Prohibition on Kratom, Allowing Consumers to Continue Lawful Use, Potential FDA Oversight, and Expanded Research

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NEWS PROVIDED BY
PinneyAssociates →
Jan 18, 2017, 10:26 ET

BETHESDA, Md., Jan. 18, 2017 /PRNewswire/ -- Kratom leaves, from a South East Asian tree in the coffee family, are often used to prepare tea-like beverages and commercially manufactured products which are consumed by several million Americans annually to increase alertness, enhance well-being and occupational performance, and as a natural remedy for minor aches and pains. **Pinney**Associates' review of the scientific evidence regarding kratom's effects is intended to assist FDA and DEA in determining the most appropriate regulatory approach within FDA authority to permit appropriate use, minimize unintended effects, encourage research, and contribute to the enhancement of public health.

DEA had proposed placing kratom in Schedule I (which includes drugs such as heroin and LSD), the most restrictive category of the Controlled Substances Act. In practical terms, this would have banned the sale of kratom and posed a major roadblock to research. The American Kratom Association petitioned the DEA to withdraw its proposal. PinneyAssociates' was then contracted to review the available information about kratom and develop an "8-factor analysis", the legal framework used to assess the abuse potential of substances, about kratom for submission to the FDA, DEA, and National Institute on Drug Abuse to inform the deliberations regarding regulation of kratom. See more about this in press coverage by Wired, Forbes, and the Washington Post.

One of the authors of the kratom 8-factor analysis was Dr. Jack Henningfield, Vice President of Research, Health Policy and Abuse Liability, at **Pinney**Associates, and Adjunct Professor of Behavioral Biology, Johns Hopkins University School of Medicine. Dr. Henningfield commented, "It's important to understand that although kratom has some mild effects similar to opioids, its chemical make-up is different, and it appears overall much safer, with apparently relatively small effects on respiration. In fact, kratom's analgesic effects and impact on energy, combined with its favorable safety profile supports continued access by consumers to appropriately regulated kratom products while research on its uses continues." Furthermore, he said "surveys suggest that kratom products are used by many former opioid users as a naural remedy to help them abstain from opioids."

Dr. Henningfield concluded, "Our work on kratom is an example of how we help regulators and industry make scientifically informed decisions about the risks and benefits of pharmaceuticals and nutritional supplements. This is a key facet of the work we produce at the intersection of science and public health policy." The kratom abuse potential assessment is an example of the comprehensive abuse potential assessments and CSA 8-factor assessments that **Pinney**Associates scientists develop for pharmaceutical companies to submit to the FDA in support of CNS-acting products including opioids, ADHD stimulants, anti-epileptics, and sedative sleep aids.

About PinneyAssociates

PinneyAssociates is a pharmaceutical and consumer healthcare consulting company that helps clients to reduce their regulatory risk and enhance the commercial value of their life sciences products. **Pinney**Associates consults with pharmaceutical companies that market a wide variety of prescription and over-the-counter medications. **Pinney**Associates' experts have extensive expertise in abuse-deterrent drug formulation evaluation, abuse potential assessment, as well as pharmaceutical risk management, Rx-to-OTC switch, and tobacco harm reduction.

For more information about **Pinney**Associates, please contact us at +1.301.718.8440 or info@pinneyassociates.com, or learn more about our work at www.pinneyassociates.com.

SOURCE PinneyAssociates

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CISION
PR Newswire

PetitionTrumpForKratom.org Site Launched To Keep Pressure Up Against Criminalization Of Herb Kratom

Fresh Off Generating 71% of All Comments Submitted During DEA Public Comment Period, American Kratom Association Responds to Outpouring of Community's Support and Desire to Use All Avenues to Keep Kratom Legal.

NEWS PROVIDED BY
American Kratom Association, Washington, D.C. →
Dec 19, 2016, 12:48 ET

WASHINGTON, Dec. 19, 2016 /PRNewswire-USNewswire/ -- Americans who don't want to see the Drug Enforcement Administration (DEA) and the Food and Drug Administration (FDA) prevail in the agencies' "war" against the coffee-like herb kratom are being urged to sign a petition to President-Elect Donald Trump at http://www.PetitionTrumpForKratom.org. The petition asks the incoming President to either halt the DEA/FDA push to criminalize kratom or to reverse any 11th hour ban that might be imposed in the waning days of the Obama Administration.

American Kratom Association

The deadline for signers to add their names to the petition is 11:59 p.m. EST on January 22, 2017. The list of those signing www.PetitionTrumpForKratom.org will be presented to President-Elect Trump in his first full business day in office: Monday, January 23, 2017.

AKA is working hard to get as many people as possible who have benefited from kratom to share their opposition to the classification by the DEA of the coffee-like herb as a Schedule I drug. Late last month, AKA released a report by a leading addiction expert who concluded that kratom has as low or even lower potential for abuse and dependence as nutmeg and St. John's Wort.

American Kratom Association Director Susan Ash said: **"The kratom community in the United States is looking for ways to continue to speak out and be heard which is why we created this additional avenue to take our message to President-Elect Trump. Supporting similar petition drives, this petition makes it quick and easy to ensure our voices continue to be heard, particularly if any action occurs before the new Administration takes office."**

Ash added: **"We are asking America's incoming leader to end the unwarranted and unfair attempt to criminalize kratom and to protect those who process and sell kratom, along with the estimated three-five million consumers who benefit from it. We urge everyone who wants to keep kratom legal to go to www.PetitionTrumpForKratom.org and sign their name."**

The petition at www.PetitionTrumpForKratom.org reads in part:

"President-elect Trump:

Your promise to end excessive government regulations and restore the limited role of government in the lives of Americans is the reason that we are appealing to you today.

The three-five million Americans who choose to use the natural herb kratom to maintain their well-being desperately need your help. We are concerned that the Drug Enforcement Administration may soon choose to curb access to this herb. If such an 'eleventh hour' step is taken during the waning days of the Obama Administration, we ask that you reverse it upon taking office. If the DEA has not acted by January 21st, we ask that you put an end to regulatory proceedings targeting kratom.

The DEA and the U.S. Food and Drug Administration have openly declared war on kratom consumers, and these agencies are blatantly abusing their powers to criminalize both those who produce and sell kratom products, and those who purchase and consume them. These federal regulators are doing all they can to deny American consumers their freedom to make individual choices on the safe products they want to use to maintain their health and well-being.

Despite credible evidence proving kratom is no more addictive than a cup of coffee, and its use presents no threat to the public health, the DEA and the FDA are continuing their efforts to classify kratom as a dangerous drug – with the same classification as heroin or cocaine.

Who are we?

We are veterans … and lawyers … and factory workers … and school teachers … and health care professionals. We are mothers and fathers … and grandparents and senior citizens.

We are the real face of America. Our choice to consume kratom does not make us "drug abusers" any more than drinking a cup of coffee would …

Unfortunately, this regulatory nightmare for millions of Americans could get worse. If kratom is effectively banned, the door will be open for the DEA and Food and Drug Administration to go on a "regulatory jihad" to prohibit hundreds of products and substances – such as nutmeg, hops, St. John's Wort, and chamomile -- now widely used by Americans. If the DEA and FDA ban kratom and take no action on other products and substances of equal or greater concern than kratom, they will be singling out kratom consumers in a grossly harsh and unbalanced manner.

A Trump Administration order for the DEA and FDA to cease the unwarranted persecution of the millions of consumers who choose to consume the botanical herb kratom would be a declaration that individual liberty will be respected in America, that consumers will have the freedom to make informed choices, and that powers of government should be restrained and used only when absolutely necessary.

We the undersigned citizens ask for your immediate action to protect our rights and our freedoms."

The American Kratom Association is proud to have been instrumental in helping to coordinate the broad-based national opposition to the DEA's attempt to effectively ban kratom. In addition to creating www.PetitionTrumpForKratom.org, AKA also:

- Led the charge when the DEA opened a comment period running through December 1st. Of the over 23,000 comments submitted before the deadline closed, the KratomComments.org Web site created by AKA was responsible for 16,379 comments – roughly 71 percent of total comments received at Regulations.gov. (The campaign Web site is now inactive.)
- Underwrote and issued on November 30th a long-awaited analysis by Dr. Jack Henningfield, Ph.D., vice president of Research, Health Policy, and Abuse Liability at PinneyAssociates, concluding that there is "insufficient evidence" for the U.S. Drug Enforcement Administration (DEA) to ban or otherwise restrict kratom under the Controlled Substances Act. According to the comprehensive Henningfield analysis, kratom's potential for abuse and dependence is as low or lower than such widely used and unscheduled substances as "nutmeg, hops, St. John's Wort, chamomile, guarana, and kola nut."
- Conducted in November 2016 an online survey of 105 emergency room (ER)/trauma health care professionals that found zero reported cases of deaths related to kratom. The new poll of America's front-line medical professionals also uncovered precisely zero percent support among those surveyed for a DEA ban on the coffee-like herb kratom.
- Encouraged a set of two letters sent on October 1st by a politically diverse group of 11 Senators, including Sen. Orrin G. Hatch (R-UT), Sen. Ron Wyden (D-OR) and Sen. Cory Booker (D-NJ), calling on the DEA to halt the proposed scheduling and allow for a regular rulemaking process permitting the public, scientific experts, and Congress to provide input.
- Facilitated letters to the DEA and the Office of Management and Budget sent on September 26th by a bipartisan group of 51 U.S. House Members urging a halt to the DEA's push to ban kratom.
- Worked with the Pain News Network on a September survey of 6150 kratom users about their experience with the herb.
- Promoted a successful and widely publicized September 13th "March for Kratom" in September at the White House.
- Circulated a "We The People" petition targeting the White House that has accumulated more than 142,000 signatures to date.

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SOURCE American Kratom Association, Washington, D.C.

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PR Newswire

American Kratom Association: Major New Analysis Shows No Basis For DEA To Restrict Herb Kratom

Expert Finds Potential for Abuse May Be As Low As Such Unrestricted Substances as "Nutmeg and St. John's Wort"

NEWS PROVIDED BY
American Kratom Association, Washington, D.C. →
Dec 01, 2016, 11:56 ET

WASHINGTON, Dec. 1, 2016 /PRNewswire-USNewswire/ -- A long-awaited analysis by one of the world's leading experts on drug abuse and addiction concludes that there is "insufficient evidence" for the U.S. Drug Enforcement Administration (DEA) to ban or otherwise restrict the coffee-like herb kratom under the Controlled Substances Act. According to the comprehensive analysis, kratom has little potential for abuse and dependence – as low or lower than such widely used and unscheduled substances as "nutmeg, hops, St. John's Wort, chamomile, guarana, and kola nut."

In preparing the report for the American Kratom Association (AKA), Dr. Jack Henningfield, Ph.D., vice president of Research, Health Policy, and Abuse Liability at PinneyAssociates, concludes: **"Kratom has a low potential for abuse and a low dependence liability and there is insufficient evidence of personal harm, adverse health effects or detriment to the public health to warrant control under the [Controlled Substances Act] . . . Appropriate regulation of kratom under the [Food, Drug, and Cosmetic Act] is the most effective way to protect the public health by ensuring appropriate access and oversight and to sustain the overall very low adverse personal and public health effects associated with kratom consumption."**

Dr. Henningfield previously served as chief of the Clinical Pharmacology Research Branch of the National Institutes of Health's National Institute on Drug Abuse (NIDA), and is currently an adjunct professor of Behavioral

Biology in the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine.

A DEA comment period on kratom closes at 12:59 p.m. EST tonight. AKA has filed its comment letter (http://bit.ly/akacomments), including the Henningfield analysis (http://bit.ly/Henningfieldreport), in the DEA public docket.

The AKA comment letter to the DEA notes: **"[K]ratom does not meet the criteria for permanent scheduling under the CSA – under schedule I or any other schedule – and DEA cannot satisfy the legal requirements for use of the emergency scheduling provision of the CSA to temporarily schedule kratom. Scheduling kratom under the CSA would divert government resources from more critical initiatives, have a significant negative impact on a substantial number of small businesses and consumers who choose to use kratom products safely and responsibly, yet yield no positive impact on the public health."**

The letter continues: **"For both abuse potential and dependence liability, kratom's profile is comparable to or lower than that of unscheduled substances such as caffeine, nicotine-containing smoking cessation products, dextromethorphan, and many antihistamines, antidepressants, and other substances sold directly to consumers. Kratom's profile also resembles that of various botanical dietary supplements such as chamomile, lavender, St. John's Wort, kava, and hops. "**

Commenting on the Henningfield analysis, Susan Ash, founder, American Kratom Association, said: **"Kratom is a natural botanical product consumed by millions of Americans daily. Like caffeine, when used responsibly, kratom is enjoyable, safe, rarely associated with any serious adverse effects, and not prone to abuse. Kratom simply does not pose an imminent threat to the public health. Rather, kratom is more reasonably characterized as a dietary supplement, and could be ably regulated as such by FDA. Through that regulatory framework, manufacturers and distributors of kratom could be held accountable for the safety and labeling of their products, while ensuring continued access to Americans who consume them. We believe such an approach would represent a much more efficient use of governmental resources than the scheduling process could provide."**

The AKA comment concludes that singling out kratom for scheduling would be inconsistent with federal handling of other supplements: **"For example, the botanical substances St. John's Wort, Valerian, and Kava**

Kava are known to have reinforcing effects and to act as sedatives, and have been the subject of hundreds or thousands of calls to Poison Control Centers. Yet, these substances have not been scheduled, but have been regulated as dietary supplements. The same is true for guarana and kola nut, which also have certain characteristics of a drug of abuse. Yohimbine, the primary component of yohimbe extract, is an indole-containing alkaloid that is structurally similar to [the active ingredient in kratom], yet yohimbe is available in the U.S. as a dietary supplement …None of these botanical substances is scheduled, despite sharing some characteristics with controlled substances; rather, all of them are adequately regulated by FDA through existing authority. Kratom, with a comparable or lower potential for abuse than these substances, would likewise be best regulated" by the FDA.

In the United States, there have been few reported serious side effects associated with kratom use and no reported deaths directly attributable to the substance. There have been *no* deaths, serious adverse effects, or emergency department visits reported for children. The relative safety of kratom is consistent with several key clinical and pharmacologic properties of the substance, including its low toxicity, extremely low bioavailability (absorption into the body), and its blocking of opioid receptors that limit the possible euphoric effect and substantially reduces the risk of respiratory depression.

Dr. Henningfield and his PinneyAssociates colleagues conducted a comprehensive review of publicly available data on the same eight factors indicative of control that the DEA and FDA will weigh in deciding if and where to control kratom:

(1) Its actual or relative potential for abuse.

(2) Scientific evidence of its pharmacological effect, if known.

(3) The state of current scientific knowledge regarding the drug or other substance.

(4) Its history and current pattern of abuse.

(5) The scope, duration, and significance of abuse.

(6) What, if any, risk there is to the public health.

(7) Its psychic or physiological dependence liability.

(8) Whether the substance is an immediate precursor of a substance already controlled through the CSA.

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SOURCE American Kratom Association, Washington, D.C.

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In Major Outpouring Of Support, 13,000 Comments Submitted To DEA Via KratomComments.org To Keep Kratom Legal

American Kratom Association Set 10,000 Comment Target to be Met by December 1st Deadline; Less Than 36 Hours to Go Before Comment Period Closes at 11:59 p.m. EST Thursday.

NEWS PROVIDED BY
American Kratom Association, Washington, D.C. →
Nov 30, 2016, 16:05 ET

WASHINGTON, Nov. 30, 2016 /PRNewswire-USNewswire/ -- As of noon EST today, the www.KratomComments.org Web site organized by the American Kratom Association (AKA) had generated 12,875 comments to the U.S. Drug Enforcement Administration (DEA) ahead of its 11:59 p.m. EST December 1st comment period deadline.

Input from KratomComments.org is cascading in so quickly into the DEA's Regulation.gov comment form that the federal agency's official count was lagging at 11,382 as of noon EST today. AKA created the KratomComments.org website in October 2016 to make it easier for consumers to submit their comments to the DEA. The site has proven so popular that 1,436 comments – more than a tenth of all comments received so far - were submitted on November 29th alone.

AKA is working hard to get as many people as possible who have benefited from kratom to share their opposition to the classification of the coffee-like herb as a Schedule I drug.

American Kratom Association Director Susan Ash said: **"We are delighted that people used what we provided to make submitting comments easier. If you've already sent your comments in to the DEA directly or**

through KratomComments.org, please make it your mission today to find five other people in the kratom community, and/or family members who have witnessed positive changes in your life as a result of kratom, and encourage them to send in comments. We need to make sure our voices cannot be ignored. I am appealing to you -- to each and every one of you with a story like my own -- to help get this done."

The KratomComments.org website simplifies the process of submitting comments to the DEA through Regulations.gov and also provides kratom community members with an assurance that there will be an independent record of their submissions – one that is not subject to federal computer problems (as were experienced shortly after the comment period opened) or any concerns about "missing" or otherwise "lost" comment submissions to the DEA.

Visitors making comments at the KratomComments.org site receive a confirmation and tracking number from the federal comment logging system. KratomComments.org operates under a strict privacy policy and only submits to the DEA the personally identifiable information that (1) the individual commenter elects to provide and (2) the DEA requires. No comments are being screened or otherwise reviewed by the organizers of KratomComments.org, which does not supply a boilerplate text or otherwise standardized comment for submitters.

The American Kratom Association is proud to have been instrumental in helping to coordinate the broad-based national opposition to the DEA's attempt to effectively ban kratom. In addition to creating KratomComments.org, AKA also:

- Conducted in November 2016 an online survey of 105 emergency room (ER)/trauma health care professionals that found zero reported cases of deaths related to kratom. The new poll of America's front-line medical professionals also uncovered precisely zero percent support among those surveyed for a DEA ban on the coffee-like herb kratom.
- Encouraged a set of two letters sent on October 1st by a politically diverse group of 11 Senators, including Sen. Orrin G. Hatch (R-UT), Sen. Ron Wyden (D-OR) and Sen. Cory Booker (D-NJ), calling on the DEA to halt the proposed scheduling and allow for a regular rulemaking process permitting the public, scientific experts, and Congress to provide input.
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SOURCE American Kratom Association, Washington, D.C.

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CISION
PR Newswire

Survey Of ER/Trauma Health Care Professionals Finds No Evidence Of Either Kratom Deaths Or Epidemic Of Abuse

Findings of American Kratom Association Poll Submitted to DEA Before December 1 Comment Period Closes; Zero Support Found Among ER/Trauma Professionals for DEA Banning Natural Herb

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NEWS PROVIDED BY
American Kratom Association, Washington, D.C. →
Nov 29, 2016, 15:14 ET

WASHINGTON, Nov. 29, 2016 /PRNewswire-USNewswire/ -- If the DEA is correct in suggesting that there is a kratom epidemic going on in America, then it is somehow happening without our nation's front-line medical professionals knowing a thing about it. A random online survey of 115 emergency room (ER) and trauma health care professionals across the U.S. found zero reported cases of deaths related to kratom. The new poll also uncovered precisely 0 percent support among those surveyed for a Drug Enforcement Administration (DEA) ban on the coffee-like herb kratom.

Available online at http://bit.ly/kratomdocpoll and conducted via SurveyMonkey, the American Kratom Association (AKA) poll was carried out between November 23-28.

AKA is submitting the survey findings as a formal response to the request for kratom-related comments from the DEA, a process that closes at 11:59 p.m. on December 1st.

American Kratom Association Founder Susan Ash said: **"We conducted this survey after ER doctors and other medical professionals told us the notion there is some kind of kratom epidemic going on in America is a hoax. In fact, our totally random online survey found no evidence of kratom-related deaths and zero support among America's front-line medical professionals for a ban on kratom. We are not going to stand idly by and let the DEA or anyone else whip up a phony panic about a nonexistent epidemic to try and ban a legal product that's being consumed responsibly, with no major problems, by three-five million Americans."**

Key survey findings include the following:

- 93 percent of those surveyed are aware of kratom.
- 89 percent of those surveyed have a favorable impression of kratom, including 81 percent with a "very favorable" impression.
- 87 percent said they would "not classify [kratom] as a problem compared to heroin and prescription painkillers." Another 5 percent said it was a "somewhat smaller" or "much smaller" problem. 0 percent said it was a "somewhat bigger" or "much bigger" problem.
- 90 percent say kratom is not a "major issue or concern" in their work experience. More than nine out of 10 ER/EMT professionals say they have never dealt with any major case involving kratom.
- 0 percent said "a ban on the herb kratom is justified based on your professional experience." About 9 percent said they did not have enough experiences with kratom to form an opinion and another 2 percent said they did not know.
- 0 percent reported deaths due to kratom and only 1 percent related any kind of health-related issues associated with the herb. According to the poll, the vast majority of times (86 percent) that kratom arises in an ER or EMT situation is when someone asks for information about kratom or reports that they consume it.

The random online survey conducted via SurveyMonkey focused on panel of ER/trauma doctors, surgeons, nurses, related health care professionals, and EMTs/paramedics. Invitations to participate in the survey were extended directly through LinkedIn groups (including EMS Leadership and Administration, Emergency Room RNs and Management, Emergency Medicine and EMS World) and Facebook groups (including Paramedics on Facebook, FRCS Trauma & Orthopedic Surgery, First Responders, Trauma, Critical Care, and Acute Care Surgery, and Emergency Medical Technician). The full results and the complete text of the survey instrument are available online at http://bit.ly/kratomdocpoll.

ABOUT AKA

The America Kratom Association, a consumer-based non-profit organization, is here to set the record straight, giving voice to those suffering and protecting our rights to possess and consume kratom. AKA represents tens of thousands of Americans, each of whom have a unique story to tell about the virtues of kratom and its positive effects on their lives. www.americankratom.org

SOURCE American Kratom Association, Washington, D.C.

Related Links

http://www.americankratom.org

CISION®
PR Newswire

In Major Outpouring Of Support, 13,000 Comments Submitted To DEA Via KratomComments.org To Keep Kratom Legal

American Kratom Association Set 10,000 Comment Target to be Met by December 1st Deadline; Less Than 36 Hours to Go Before Comment Period Closes at 11:59 p.m. EST Thursday.

NEWS PROVIDED BY
American Kratom Association,
Washington, D.C. →
Nov 30, 2016, 16:05 ET

WASHINGTON, Nov. 30, 2016 /PRNewswire-USNewswire/ -- As of noon EST today, the www.KratomComments.org Web site organized by the American Kratom Association (AKA) had generated 12,875 comments to the U.S. Drug Enforcement Administration (DEA) ahead of its 11:59 p.m. EST December 1st comment period deadline.

Input from KratomComments.org is cascading in so quickly into the DEA's Regulation.gov comment form that the federal agency's official count was lagging at 11,382 as of noon EST today. AKA created the KratomComments.org website in October 2016 to make it easier for consumers to submit their comments to the DEA. The site has proven so popular that 1,436 comments – more than a tenth of all comments received so far - were submitted on November 29th alone.

AKA is working hard to get as many people as possible who have benefited from kratom to share their opposition to the classification of the coffee-like herb as a Schedule I drug.

American Kratom Association Director Susan Ash said: **"We are delighted that people used what we provided to make submitting comments easier. If you've already sent your comments in to the DEA directly or through KratomComments.org, please make it your mission today to find five other people in the kratom community, and/or family members who have witnessed positive changes in your life as a result of kratom, and encourage them to send in comments. We need to make sure our voices cannot be ignored. I am appealing to you -- to each and every one of you with a story like my own -- to help get this done."**

The KratomComments.org website simplifies the process of submitting comments to the DEA through Regulations.gov and also provides kratom community members with an assurance that there will be an independent record of their submissions – one that is not subject to federal computer problems (as were experienced shortly after the comment period opened) or any concerns about "missing" or otherwise "lost" comment submissions to the DEA.

Visitors making comments at the KratomComments.org site receive a confirmation and tracking number from the federal comment logging system. KratomComments.org operates under a strict privacy policy and only submits to the DEA the personally identifiable information that (1) the individual commenter elects to provide and (2) the DEA requires. No comments are being screened or otherwise reviewed by the organizers of KratomComments.org, which does not supply a boilerplate text or otherwise standardized comment for submitters.

The American Kratom Association is proud to have been instrumental in helping to coordinate the broad-based national opposition to the DEA's attempt to effectively ban kratom. In addition to creating

KratomComments.org, AKA also:

- Conducted in November 2016 an online survey of 105 emergency room (ER)/trauma health care professionals that found zero reported cases of deaths related to kratom. The new poll of America's front-line medical professionals also uncovered precisely zero percent support among those surveyed for a DEA ban on the coffee-like herb kratom.
- Encouraged a set of two letters sent on October 1st by a politically diverse group of 11 Senators, including Sen. Orrin G. Hatch (R-UT), Sen. Ron Wyden (D-OR) and Sen. Cory Booker (D-NJ), calling on the DEA to halt the proposed scheduling and allow for a regular rulemaking process permitting the public, scientific experts, and Congress to provide input.
- Facilitated letters to the DEA and the Office of Management and Budget sent on September 26th by a bipartisan group of 51 U.S. House Members urging a halt to the DEA's push to ban kratom.
- Worked with the Pain News Network on a September survey of 6150 kratom users about their experience with the herb.
- Promoted a successful and widely publicized September 14th "March for Kratom" in September at the White House.
- Circulated a "We The People" petition targeting the White House that has accumulated more than 142,000 signatures to date.

ABOUT AKA

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SOURCE American Kratom Association, Washington, D.C.

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http://www.americankratom.org

CISION
PR Newswire

American Kratom Association: DEA Push To Schedule Natural Herb Kratom Will Harm Veterans, Seniors And Other Americans

Hundreds of Thousands of Kratom Consumers Have Urged DEA to Stop Classification of Coffee-Like Botanical As a Major Narcotic; 51 Members of Congress Urge DEA to Respect Due Process

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NEWS PROVIDED BY
American Kratom Association, Washington, D.C. →
Sep 28, 2016, 16:07 ET

WASHINGTON, Sept. 28, 2016 /PRNewswire-USNewswire/ -- The American Kratom Association (AKA) supports the legal use of kratom by millions of Americans. The Association believes that kratom should not be classified as a Schedule 1 drug by the Drug Enforcement Administration (DEA). In the words of AKA Founder Susan Ash: "Veterans, grandparents, and mature adults in all fields including medical and law enforcement are utilizing this herb safely and responsibly. They now are facing the possibility of becoming felons for simply choosing a natural plant over pharmaceutical drugs."

The American Kratom Association disagrees vehemently with the DEA's proposed action. AKA would embrace an open process where the facts can be presented and explored. A thorough scientific review and citizen's testimony may lead to some new regulations. However, the current DEA intention is NOT the answer and could prove harmful.

AKA Executive Director Paul Pelosi, Jr. explained: "At this challenging moment, it is important to remember why we started supporting one's right to kratom. For me, I recall my conversations with veterans like U.S Army veteran David Dasilma and his personal story about how his life improved when he switched from exorbitantly priced prescription drugs to the natural leaf."

Pelosi emphasized: "We Americans who believe in the 10th Amendment are marching and supporting kratom lovers. We have the right to herbal supplements. We pray federal agencies will either leave the leaf alone or work with the public to craft a solution that ensures long term availability of safe, affordable, and effective access to kratom."

The AKA worked last week with Members of the US House of Representatives, who circulated a "Dear Colleague" letter that now bears the signatures of 51 Members of Congress. The full text of the letter is available here: https://www.scribd.com/document/325084831/Dear-Colleague-for-Kratom-Letters-to-Outside-Organizations#download. An additional letter may be circulated among members of the U.S. Senate.

The American Kratom Association and other industry advocates have volunteered considerable time, energy and resources to provide credible scientific data and consumer testimonials to law makers nationally and in over 20 states. AKA board members like Angela Ross make time to educate the public. As she noted: "I am deeply passionate about keeping this plant legal because I am living proof of what it can do. That is why I educate people about this leaf."

In light of DEA's intention, the AKA has encouraged members and concerned citizens to express their opinions regarding the safe and effective use kratom. Association Board Member Robin Graham reminds us: "The AKA has been and will continue to be the voice of strength and reason in this fight for kratom. Making felons of those who drink a cup of tea is not and will never be ok. Prohibition has not worked in the past and will not work in the future. It is time to allow common sense to lead the way, not fear or misguided personal agendas."

AKA's strong and clear voice in support of kratom has been documented so far in nearly 150 news stories – including coverage in the Washington Post, Newsweek, Huffington Post, National Public Radio and USA Today -- because of four grassroots efforts:

1. Members and many others initiated marches in Washington and around the country in support of keeping kratom legal for consumer use and medical research.

2. An outpouring of 130,000 veterans, seniors, disabled individuals and

other Americans signed a petition to the White House asking President Obama to stop the DEA from proceeding with a ban on the basis of no regard for science and even less for due process.

3. More than 6,000 people were enlisted by AKA to participate in a Pain News Network survey detailing their effective uses for kratom.

4. Thousands AKA members have been e-mailing and calling their Congress members and Senators to intervene and helped get 51 signatures on a bipartisan "Dear Colleague in the House" letter asking the DEA to stop this emergency action.

The AKA is thankful to the public supporting the protest of government action restricting access to kratom. As AKA board member Paul Kemp likes to say: "I prefer the natural leaf over prescription drugs. Since there is no substantial finding of harm caused by the leaf, I will fight for the freedom to use kratom."

The America Kratom Association (AKA), a consumer-based non-profit, is here to set the record straight, giving voice to the suffering and our rights to possess and consume kratom. AKA represents tens of thousands of Americans; each with a unique story to tell about the virtues of kratom and its positive effects on our lives. From Lyme Disease to Post Traumatic Stress Disorder and even addiction, kratom can help offer relief.
www.americankratom.org

SOURCE American Kratom Association, Washington, D.C.

Related Links

http://www.americankratom.org

MEMORANDUM

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TO	David Herman Chair, Board of Directors	**ORGANIZATION**	American Kratom Association
FROM	Lynn W. Mehler Delia A. Deschaine	**TELEPHONE**	202-637-6419
DATE	June 21, 2017		
SUBJECT	Analysis of the Stop the Importation and Trafficking of Synthetic Analogues Act of 2017 (SITSA)		

Per your request, please find below our analysis of SITSA and its implications on the regulated community. In sum, we believe that the scope of the law far exceeds its stated intent: the control of fentanyl analogs and other synthetic substances that pose a high potential for abuse.

- Under the current Controlled Substances Act (CSA), DEA has ample authority to immediately control substances with a high potential for abuse. DEA has appropriately exercised this authority to control fentanyl and other synthetic analogs in the past. For example, DEA has temporarily placed at least fifteen fentanyl analogs in Schedule I through the use of its emergency scheduling authority. When enacting the CSA, Congress wisely chose to authorize DEA to temporarily control only those substances that have a high potential for abuse, by requiring their placement in Schedule I.

- SITSA as drafted contains broad language that would allow DEA to control substances with low abuse potential based purely on these substances chemical similarity to lower schedule (Schedule V) controlled substances. Specifically, the law would allow DEA to temporarily and permanently control a drug or substance with a chemical structure that is substantially similar to that of a Schedule V controlled substance and an actual or predicted stimulant, depressant or hallucinogenic effect on the central nervous system that is substantially similar to that of Schedule V controlled substance. In determining the latter, DEA *may,* but is not required to consider a number of factors, one of which is "the chemical structure, structure activity relationships, binding receptor assays, or other relevant scientific information about the substance." As DEA's authority would remain unchecked (there is no requirement or process to allow for public comment or judicial review for a period of at least five years), DEA may succeed in using this authority to control substances with low or no abuse potential, such as Kratom, based purely on the substance's chemical properties.

- SITSA would allow DEA to sweep in substances that pose no actual abuse potential and precedent indicates DEA would take full advantage of the broad language in the legislation. For example, the current CSA controls in Schedule II any salt, compound, derivative or preparation which is chemically equivalent or identical with opium, an opiate, or any salt, compound, derivative or preparation of opium or opiate. DEA's broad interpretation and application of these provisions has swept a number of substances into Schedule II based on their chemical relationship to opioids, regardless of whether the substance has any abuse potential. For example, naloxegol was controlled in Schedule II as a result of its chemical relationship to an opiate. In 2015, DEA removed the drug from control after FDA approval, as it lacked a potential for abuse sufficient to schedule the drug in any schedule. *See* 80 Fed. Reg. 3468 (Jan. 23, 2015). *See* 79 FR 64349, 64350 (Oct. 29, 2014) (Naloxegol, or PEG-naloxol, is a new molecular entity and is a polyethylene glycolyated (PEGylated) derivative of naloxone . . . Naloxegol is an antagonist predominantly of peripheral mu opioid receptors).

- SITSA as drafted would significantly expand the universe of drugs or substances that DEA could immediately control with little notice to legitimate stakeholders or input from experts and with few curbs on the authority of DEA. In so doing, the proposed law would give DEA the unfettered ability to eliminate access to such substances, despite what may be long-standing and legitimate non-medical uses (*e.g.*, industrial uses, uses in foods, uses in dietary supplements) and would substantially curtail and burden legitimate scientific research and product development. Furthermore, despite the reference to synthetic analogues in the title of the legislation, the legislative language is so broad as to sweep in a range of drugs or substances.

- SITSA as drafted would further allow DEA to control such substances for a period of five years, without providing interested members of the public any due process to challenge the DEA conclusions and removal of the substance from legitimate commerce. The length of time for such a "temporary" scheduling along with the absence of any opportunity for judicial review or public participation renders this provision of SITSA unconstitutional.

- Even if extending the period of temporary control without public participation were constitutional, Congress could do so simply by amending the existing temporary control provisions of the CSA, as it has in the past. *See* Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 1153 (2012). Congress does not need to also lower the standard for temporarily controlling substances to include substances with a low potential for abuse.

- The proposed law would schedule substances with a potential for abuse that are substantially similar to Schedule V controlled substances, however, would attach penalties comparable to those that apply to Schedule III controlled substances for the unlawful manufacture, distribution, or dispensing of those substances. It is not clear why the penalties that apply to the illicit use of such analogs should be more stringent than they are for their controlled counterparts.

- The attached proposed revisions may correct some but not all of the flaws of the proposed law described above. As a whole, the proposed law is unnecessary, unjustified and unconstitutional.

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Docket No. DEA-442W

November 30, 2016

Michael J. Lewis
Office of Diversion Control
U.S. Drug Enforcement Administration
8701 Morrissette Drive
Springfield, Virginia 22152

Re: Mitragynine and 7-Hydroxymitragynine, Constituents of the Kratom Plant, Should Not Be Scheduled under the Controlled Substances Act

Dear Mr. Lewis:

We write on behalf of our client, the American Kratom Association, to oppose the scheduling of mitragynine and 7-hydroxymitragynine, constituents of the kratom plant,[1] under the Controlled Substances Act (CSA).[2] Kratom is a botanical substance that has been safely and responsibly consumed for its mild caffeine-like effects for centuries in Southeast Asia and for at least two decades in the United States. The Drug Enforcement Agency (DEA) has solicited comments regarding the potential scheduling of kratom under the CSA and, should DEA determine that kratom should be scheduled, the statutory scheduling process DEA should pursue.

As discussed more fully below, kratom does not meet the criteria for permanent scheduling under the CSA – under schedule I or any other schedule – and DEA cannot satisfy the legal requirements for use of the emergency scheduling provision of the CSA to temporarily schedule kratom. Scheduling kratom under the CSA would divert government resources from more critical initiatives, have a significant negative impact on a substantial number of small businesses and consumers who choose to use kratom products safely and responsibly, yet yield no positive impact on the public health. Rather, kratom can be appropriately regulated by the Food and Drug Administration (FDA) through existing authority under the Food, Drug, and

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[1] The DEA notice requests comments on the scheduling of mitragynine and 7-hydroxymitragynine, two constituents of kratom. For simplicity, we refer to these constituents collectively as "kratom," understanding that mitragynine and 7-hydroxymitragynine are only two of many alkaloids and other constituents that constitute the kratom plant.

[2] 21 U.S.C. § 801 *et seq.*

Cosmetic Act (FDCA) to ensure the safe and appropriate use of consumer kratom products as traditionally marketed in the U.S.

With this letter we are also submitting an eight factor analysis[3] and scheduling recommendation by Jack Henningfield, Ph.D., Vice President of Research, Health Policy, and Abuse Liability and his colleagues at PinneyAssociates. Dr. Henningfield is one of the world's leading experts on drugs of abuse, addiction, and the assessment of the abuse liability of various substances. Among other positions, he served as Chief of the Clinical Pharmacology Research Branch of the National Institutes of Health's National Institute on Drug Abuse (NIDA), and is currently an Adjunct Professor of Behavioral Biology in the Department of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine. Dr. Henningfield and his colleagues conducted a comprehensive review of publicly available data on the eight factors indicative of the need for control under the CSA.

Dr. Henningfield's analysis, *Kratom under the CSA Eight Factors and Scheduling Recommendation* (attached) concludes:

> Kratom has a low potential for abuse and a low dependence liability and there is insufficient evidence of personal harm, adverse health effects or detriment to the public health to warrant control under the CSA. . . . Appropriate regulation of kratom under the FDCA is the most effective way to protect the public health by ensuring appropriate access and oversight and to sustain the overall very low adverse personal and public health effects associated with kratom consumption."[4]

This letter details the scientific and statutory grounds for these conclusions.

I. FACTUAL BACKGROUND

A. American Kratom Association

The American Kratom Association (AKA) is a non-profit organization representing responsible members of the public who consume kratom products for improved health and well-being. AKA provides the general public, lawmakers, and regulators with information about kratom's history of safe use and supports scientific research to increase understanding of this

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[3] As discussed in more detail below, the CSA requires a thorough analysis by the Attorney General, acting through DEA and in conjunction with HHS, of the eight factors listed in section 811(c) for any drug or substance with a potential for abuse to determine if the drug or substance should be placed in one of the CSA's five schedules. The analysis that results is known as an eight factor analysis.

[4] PinneyAssociates, *Kratom under the CSA Eight Factors and Scheduling Recommendation* (Nov. 28, 2016) ("Henningfield Eight Factor Analysis"). Many of these concepts are also discussed at more length in our letter of September 26, 2016, to DEA submitted in response to the DEA Notice of Intent to temporarily place mitragynine and 7-hydroxymitragynine in schedule I (attached) ("September 26 Letter").

ancient natural botanical. AKA shares the concern of many of the affected stakeholders in ensuring that the supply of kratom is safe, appropriately marketed, and consumed responsibly.

B. Kratom

Kratom (*Mitragyna speciosa*) is a deciduous tree of the coffee family (*Rubiaceae*). The kratom tree grows abundantly in tropical Southeast Asia, especially Vietnam and Malaysia. Kratom has been used for hundreds of years by the indigenous people of Southeast Asia as an herbal supplement and traditional remedy. Indeed, in that region of the world, kratom "is a part of the way of life, embedded in local custom and tradition."[5] The leaves of the plant are typically chewed, steeped into a hot tea, or dried and added as a powder to other foods or beverages. A small amount of powder may also be placed in a capsule and swallowed with water. Smoking and nasal insufflation of the leaves is less common, probably because of kratom's low bioavailability and low potency.[6] Used in a responsible way and in moderate amounts, kratom has been reported to provide increased energy and an improved sense of well-being.

Today, millions of people in the United States consume kratom regularly, as they do other herbal supplements and traditional remedies.[7] Kratom sales to consumers total approximately $207 million annually.[8] Data suggest that kratom sales account for approximately 20% of a total revenue of $1.13 billion per year as reported by small business owners operating in the botanical market.[9] Industry estimates and surveys indicate that there are approximately 10,000 kratom vendors operating in the United States market, employing some 2,500 people.[10]

Kratom users in the United States report that they primarily consume the substance for its perceived effects that enhance well-being, occupational performance, and social interactions, similar to the reasons that prompt many people to consume caffeinated beverages. Some use kratom as a natural "home remedy" that is preferred to conventional medicines because of its low rate of adverse events.[11] Others choose to use kratom on their own volition to help them

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[5] Trakulsrichai, S et al., *Pharmacokinetics of Mitragynine in Man*, 9 Drug Design, Dev. and Therapy 2421, 2422 (2015).

[6] Henningfield Eight Factor Analysis at 33-34. Mitragynine's bioavailability is approximately 3% when taken orally. *Id*. at 30; Ulbricht, C et al., *An Evidence-Based Systematic Review of Kratom (Mitragyna speciosa) by the Natural Standard Research Collaboration*, 10 J. Dietary Supplements, 152, 163 (2013).

[7] Henningfield Eight Factor Analysis at 45, 48-49, 54-55.

[8] Data compiled by the Botanical Education Alliance through a survey sampling of businesses operating in the kratom industry; September 2016. The data is accessible at https://www.botanical-education.org/wp-content/uploads/2016/09/BEA-Economic-Impact-Report_V3.pdf.

[9] *Id.*

[10] *Id.*

[11] Henningfield Eight Factor Analysis at 17, 46.

abstain from the use of other substances perceived as addictive or causing harm, such as opioids, benzodiazepines, and antidepressants.[12] As a result, these consumers avoid substances with far greater toxicity, dependence liability, and potential for abuse.

Kratom has a long history of use with few reports of confirmed adverse events. Despite its widespread use in Southeast Asia, serious adverse events have rarely been associated with kratom usage in the region.[13] Likewise, in the United States, there have been few reported serious side effects associated with kratom use and no reported deaths directly attributable to the substance.[14] Moreover, there have been *no* deaths, serious adverse effects, or emergency department visits reported for children.[15] The relative safety of kratom is consistent with several key clinical and pharmacologic properties of the substance, including its low toxicity, extremely low bioavailability, and its competing antagonist activity at the opioid receptors that limits the possible euphoric effect and substantially reduces the risk of respiratory depression. Kratom's history of safe use and its pharmacological characteristics are described in the September 26 Letter and in Dr. Henningfield's report, both of which are attached.

C. The Notice of Intent to Schedule Mitragynine and 7-Hydroxymitragynine, the Withdrawal of the Notice, and Solicitation of Comments

On August 31, 2016, DEA published a notice in the Federal Register announcing its intent to control mitragynine and 7-hydroxymitragynine by placing them into schedule I pursuant to the temporary or "emergency" scheduling provision of the CSA.[16] Following publication of the intent to schedule kratom under the emergency scheduling authority, DEA received a groundswell of opposition to its intended action in the form of comments from the public and letters from members of both houses of Congress.[17] On October 13, 2016, the agency withdrew its notice of intent and initiated a period of public comment through December 1, 2016.[18] After receipt and consideration of the comments submitted to the docket, and FDA's scientific and medical evaluation and scheduling recommendation,, DEA will determine whether to proceed with scheduling of kratom and if so, whether to follow the emergency or administrative procedures.

II. LEGAL STANDARDS

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[12] *Id*. at 19, 43-44.

[13] *Id*. at 51; Ulbricht et al. at 157; Trakulsrichai et al. at 2422.

[14] *See* Boyer, EW et al., *Self-treatment of opioid withdrawal using Kratom* (*Mitragynia speciosa korth*), 103 Addiction 1048-50 (2008) ("Although mitragynines agonize mu-opioid receptors, respiratory depression, coma, pulmonary edema and death have not, to our knowledge, been associated with human Kratom ingestion.").

[15] Henningfield Eight Factor Analysis at 16.

[16] 81 Fed. Reg. 59929 (Aug. 31, 2016).

[17] *See, e.g.*, Eric Boodman, *DEA May Reconsider Its Ban on Herbal Painkiller Kratom*, Scientific American (Oct. 6, 2016).

[18] 81 Fed. Reg. 70652, 70653 (Oct. 13, 2016).

A. Permanent Scheduling

The CSA provides a multi-factorial framework for determining whether a substance should be permanently scheduled through an administrative process set out in the statute. Specifically, DEA requests a scientific and medical evaluation and scheduling recommendation from HHS,[19] which must include analysis of the following eight factors:

(1) Its actual or relative potential for abuse.

(2) Scientific evidence of its pharmacological effect, if known.

(3) The state of current scientific knowledge regarding the drug or other substance.

(4) Its history and current pattern of abuse.

(5) The scope, duration, and significance of abuse.

(6) What, if any, risk there is to the public health.

(7) Its psychic or physiological dependence liability.

(8) Whether the substance is an immediate precursor of a substance already controlled through the CSA.[20]

Any findings by HHS regarding scientific and medical matters are binding on DEA.[21]

In addition to the eight factors, a substance must be found to meet three findings required for placement in a particular schedule. These findings relate to the substance's abuse potential, physical or psychological dependence liability, and accepted medical use in the U.S. Substances in schedule I must be found to have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.[22] Courts have specifically held that the finding of a high potential for abuse is required – as a matter of law, a substance that does not have a high potential for abuse cannot be placed into schedule I.[23]

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[19] 21 U.S.C. § 811(b). Section 811(b) provides that the scientific and medical evaluation and scheduling recommendation shall be conducted by the Secretary of the U.S. Department of Health and Human Services (HHS). This function has been delegated to the Assistant Secretary for Health. 58 FR 35460 (July 1, 1993). Within HHS, FDA has primary responsibility for conducting the evaluation and making the recommendation. *See* 81 Fed. Reg. 70653 n.2 (Oct. 13, 2016). Under an interagency Memorandum of Understanding (MOU), FDA and NIDA develop the medical and scientific evaluation and consider the appropriate factors and scheduling criteria before collaborating on a recommendation as part of the drug scheduling process. MOU 225-85-8251 (Dec. 11, 1984), *available at* http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm116365.htm. The MOU describes procedures for sharing information between the agencies and outlines FDA's role in preparing the initial recommendation and eight-factor document. Upon completion, the document is reviewed by the Assistant Secretary for Health, who makes the final determination on behalf of the Secretary.

[20] 21 U.S.C. § 811(c).

[21] *Id.* at § 811(b).

After considering the eight factors and making the required findings, HHS makes a recommendation as to the appropriate schedule for the substance. Provided HHS recommends scheduling, DEA then performs its own analysis of the eight factors. If it determines that substantial evidence of a potential for abuse exists, DEA next initiates proceedings for control of the substance through rulemaking on the record, with an opportunity for public comment and an opportunity for a hearing pursuant to the rulemaking procedures set out in the Administrative Procedures Act (APA).[24]

B. Temporary or "Emergency" Scheduling

The CSA authorizes the Attorney General, acting through DEA, to exercise emergency scheduling authority when the agency finds such scheduling "is necessary to avoid an imminent hazard to the public safety."[25] The expedited procedure permits DEA to bypass the full administrative scheduling process set out above, on an "emergency" basis, without the analysis, findings, and opportunity for public participation otherwise required by the CSA.[26] The provision was added to the statute at DEA's request in 1984 to permit an immediate response to the emergence of novel synthetic drugs on the illicit market.[27] An "imminent hazard" exists when the exercise of the full administrative process "would result in a large number of deaths and injuries or the continuance of an uncontrolled trafficking situation."[28] In determining whether an imminent hazard to the public safety exists, DEA must explicitly consider three factors:

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[22] *Id.* at § 812(b)(1).

[23] In *Grinspoon, v. DEA*, 828 F.2d 881 (1st Cir. 1987), the First Circuit found that all three findings, including the finding of a high potential for abuse, are necessary before a substance may be scheduled: "The CSA… requires substances identified for placement in Schedule I to have a 'high potential for abuse,'" *Grinspoon*, 828 F.2d at 892. The court also found that the statute "clearly provides that a substance may not be placed in Schedule I unless it lacks both a 'currently accepted medical use in treatment in the United States' and 'accepted safety for use… under medical supervision.'" *Id.* at 887; *see also Americans for Safe Access v. DEA*, 706 F.3d 438, 442 (D.C. Cir. 2013) (holding that marijuana could not be placed into Schedule III, IV, or V, regardless of its abuse potential, because it lacked one of the three required factors, "a currently accepted medical use").

[24] 21 U.S.C. § 811(a), (b).

[25] *Id*. at § 811(h)(1).

[26] *Id.* at § 811(h).

[27] *See* Pub. L. 98-473, Tit. II, §§ 508, 509(a) (Oct. 12, 1984); *see also Diversion of Prescription Drugs to Illegal Channels and Dangerous Drug Diversion Control Act: Hearing on H.R. 4698 Before the H. Comm. on the Judiciary*, 98th Cong. 401-04 (1984) (letter of Francis M. Mullen, Jr., Administrator, DEA) ("Mullen Letter").

[28] Mullen Letter at 401.

(1) the substance's history and current pattern of abuse

(2) the scope, duration, and significance of abuse and

(3) what, if any, risk there is to the public health.[29]

The analysis must also include the substance's actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution.[30]

III. KRATOM DOES NOT MEET THE CRITERIA FOR PLACEMENT IN SCHEDULE I

As discussed above, for a substance to be placed in schedule I it must be found to have a *high potential for abuse*. As discussed in detail in the attached Henningfield Eight Factor Analysis, kratom has a low potential for abuse similar to or lower than that of many other unscheduled substances including caffeinated drinks and nicotine smoking cessation products, as well as herbal products with some abuse liability including nutmeg, hops, St. John's Wort, chamomile, guarana, and kola nut. In that essential regard, kratom does not meet the legal standard for placement in schedule I.

Abuse of a drug or other substance is characterized by self-administration due to central nervous system effects that are typically reinforcing and often pleasant, yet associated with harm. Kratom's pharmacology does not predict a high risk for abuse: its only partial agonist activity, specificity to the human μ-opioid receptor, antagonist activity to the δ- and κ-opioid receptors, and mechanism of action are all consistent with other partial agonists that "display less respiratory depression, tolerance development, and constipation" than typical substances of abuse.[31] Kratom's observed patterns of use confirm the prediction of its pharmacology that the substance does not present a high risk for abuse. Kratom use in the United States is notable for the absence of typical indicia of abuse, such as impaired control over use, compulsive use, and continued use despite harm. Furthermore, there has been a notable absence of reports of dose escalation or tolerance development, which are typical indicators of substance abuse. Unlike with many substances of high abuse potential (e.g. prototypic opioids), increasing the dose of kratom does not significantly enhance mood or other perceived benefits; rather, an increased dose of kratom is more likely to cause unpleasant gastrointestinal effects, constipation, and lethargy.[32] Use history shows that kratom consumers have not engaged in extraction, injection, nasal insufflation, or smoking, and the structure of the plant is such that extraction would be very difficult, due to the low alkaloid content, low bioavailability, and high ratio of cellulose fibers in kratom. While Dr. Henningfield noted that mitragynine shows some evidence of discriminative and reinforcing effects when injected at very high doses in animals equivalent to consuming 500 to 1,000 bottles at a time, these effects would be nearly impossible to reproduce in humans because of the difficulty of isolating mitragynine from kratom leaves and mitragynine's extremely low bioavailability (about 3%).[33] Finally, anecdotal evidence indicates that the vast majority of kratom consumption is for social or occupational enhancement or an improved sense of well-being, and not for euphoric effects or getting "high."[34] When all of the evidence is considered, it is clear that kratom cannot reasonably be viewed as a substance with a high potential for abuse and, in fact, more closely resembles other unscheduled, naturally-derived substances such as caffeine. As such, kratom does not meet the criteria for placement in schedule I.

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[29] 21 U.S.C. § 811(h)(3).

[30] *Id.*

[31] Kruegel, A.C. et al., *Synthetic and Receptor Signaling Explorations of the* Mitragyna *Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators*, 138 J. Am. Chem. Soc. 6754 (2016).

[32] *See* Henningfield Eight Factor Analysis at 34.

Schedule I also requires a finding that the drug or other substance has no currently accepted medical treatment in the United States and that there is a lack of accepted safety for use of the drug or other substance under medical supervision.[35] The currently accepted medical use of a pharmaceutical drug is often straightforward, and DEA can easily establish whether a pharmaceutical drug has a currently accepted use in treatment of patients. Less clear is how this criterion may be applied to a non-pharmaceutical substance, such as a dietary supplement. A dietary supplement is a product intended to supplement the diet that contains certain types of ingredients, including botanical ingredients, and is not approved or authorized for investigation as a drug.[36] Consistent with the regulatory scheme of the FDCA, a dietary supplement is not marketed with claims of efficacy for medical use – indeed, if a dietary supplement included such claims it would likely meet the standards for regulation as a drug product under the FDCA.[37] As such, the "currently accepted medical treatment" criterion is plainly inapplicable to dietary supplements like kratom.

DEA need not wrestle with the difficult issue of how to apply the second and third required findings for schedule I to a dietary supplement such as kratom, because placing kratom into schedule I is foreclosed by the first required finding. As discussed above, "a drug or other substance may not be placed" into schedule I unless DEA finds that the substance "has a high potential for abuse."[38] Kratom does not have a high potential for abuse, as fully characterized in the Henningfield Eight Factor Analysis, because it is not used in large or escalating doses, is not used for euphoric effects, and is not used to the harm or detriment of consumers. Thus, DEA need not reach the other findings for schedule I; kratom's lack of a high potential for abuse forecloses its placement in schedule I.

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[33] *See id.* at 55.

[34] *See id.* at 46.

[35] 21 U.S.C. § 812(b)(1).

[36] *Id*. at § 321(ff).

[37] *See id.* at §§ 321(g)(1), 355(a).

[38] *Id.* at § 812(b); *Grinspoon*, 828 F.2d at 892; *Americans for Safe Access*, 706 F.3d at 442.

IV. KRATOM DOES NOT MEET THE CRITERIA FOR PLACEMENT IN SCHEDULES II-V

A full analysis of the eight factors that must be considered in a scheduling determination demonstrates that kratom should not be placed in schedules II - V either. As discussed in detail in the attached Henningfield Eight Factor Analysis, kratom's potential for abuse and dependence liability are comparable to, or lower than, that of a wide variety of unscheduled substances. Consumers use kratom for its perceived caffeine-like benefits to occupational performance and attentiveness, and not for euphoric effect. Typical use patterns are not consistent with abuse, nor are kratom products susceptible to extraction of alkaloids or abuse through injection, nasal insufflation, or smoking. No evidence has demonstrated physical dependence and withdrawal at levels consistent with human use, and the modest effects at high doses make such a heroic effort extremely unlikely. For both abuse potential and dependence liability, kratom's profile is comparable to or lower than that of unscheduled substances such as caffeine, nicotine-containing smoking cessation products, dextromethorphan, and many antihistamines, antidepressants, and other substances sold directly to consumers. Kratom's profile also resembles that of various botanical dietary supplements such as chamomile, lavender, St. John's Wort, kava, and hops. The attached Henningfield Eight Factor Analysis, which closely examines kratom's abuse potential and dependence liability, strongly counsels against scheduling kratom or its components.[39] These eight factors are considered in detail in the attached report, and briefly reviewed below.

A. Kratom's Actual or Relative Potential for Abuse

As discussed above, kratom is not associated with many of the typical indicia of abuse and carries little potential for abuse because of its low bioavailability and limited euphoric effect. In contrast to the effects of increasing the dose of substances of high abuse potential (such as opioids, stimulants, or sedatives), increasing the dose of kratom is more likely to produce undesirable gastrointestinal effects, constipation, and lethargy, with little additional mood enhancement.[40] Although the main alkaloid in kratom, mitragynine (MG), has shown some evidence consistent with abuse potential in animal studies, the abuse potential has only been observed when MG is injected and when the doses are extraordinarily high – far beyond what a human could reasonably consume (equivalent to drinking over 500 commercially available bottles of kratom in a single sitting).[41] Additionally, use patterns in kratom consumers show only modest consumption that is for kratom's perceived benefits of alertness and occupational effects, not euphoria. This central factor – a substance's potential for abuse – weighs strongly against the need for scheduling kratom.

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[39] Scheduling of kratom and its components in schedules II, III, IV, or V is also legally precluded because of kratom's lack of a currently accepted medical use. *See* Henningfield Eight Factor Analysis at 61-63. This only underscores the conclusion of Dr. Henningfield's Eight Factor Analysis that kratom is comparable to other unscheduled products and best regulated under the FDCA, rather than controlled pursuant to the CSA.

[40] *See* Kratom and Other Mitragynines The Chemistry and Pharmacology of Opioids from a Non-Opium Source (Raffa, RB, ed., 2014), pp 309–319 Boca Raton, FL: CRC; Henningfield JE, Written Summary of Oral Testimony for the State of Wisconsin Controlled Substances Board, available from http://dsps.wi.gov/Documents/Board%20Services/Agenda%20Materials/Controlled%20Substances/2015/20150814_CSB_Additional_Material.pdf (accessed Nov. 16, 2016); Ward J, Rosenbaum C, Hernon C, McCurdy CR, Boyer EW, *Herbal medicines for the management of opioid addiction: safe and effective alternatives to conventional*

B. Scientific Evidence of the Substance's Pharmacological Effect

Although there are few studies of mitragynine or 7-hydroxymitragynine (7-OH-MG) in humans, a recent study showed that mitragynine acted as only a partial agonist at human μ-opioid receptors.[42] In contrast, at human κ-opioid receptors, mitragynine was a competitive antagonist, fully inhibiting the activity of the reference agonist U-50,488.[43] Similarly, mitragynine acted as an antagonist at human δ-opioid receptors, but with very low potency.[44] 7-hydroxymitragynine was also characterized and found to be a potent, partial agonist at human μ-opioid receptors and a competitive antagonist at both human κ-opioid receptors and δ-opioid receptors.[45] The partial agonist activity of MG and 7-OH-MG at the human receptors was further confirmed in antagonist experiments, as both compounds were able to partially inhibit the response elicited by the full agonist [D-Ala2, N-Me-Phe4, Gly-ol5]-enkephalin.[46] The partial agonist activity of MG and 7-OH-MG is consistent with the lack of observed respiratory depression in kratom consumers.[47]

C. The State of Current Scientific Knowledge Regarding the Substance

While current scientific understanding of kratom would benefit from further study, some information about its pharmacodynamics and observed effects is available. Kratom components MG and 7-OH-MG have a half-life *in vivo* of about 3.5 and 2.5 hours, respectively, and are

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pharmacotherapy? 25 CNS Drugs 999-1007 (2011); Warner ML, Kaufman NC, Grundmann O, *The pharmacology and toxicology of kratom: from traditional herb to drug of abuse*, 130 Int'l. J. Legal Med. 127-38 (2016).

[41] *See* Harun et al., 2015; Henningfield Eight Factor Analysis at 23-24.

[42] Kruegel et al., 2016.

[43] *Id.*

[44] *Id.*

[45] *Id.*

[46] *Id.*

[47] *See* Macko E, Weisbach JA, Douglas B, *Some observations on the pharmacology of mitragynine*, 198 Archives Internationales de Pharmacodynamie et de Therapie 145-51 (1972).

primarily eliminated in urine.[48] MG and 7-OH-MG have produced responses consistent with mild analgesic effect in rodents.[49] Observations in humans have shown mild stimulant effects, as well as alertness and sociability.[50] At higher doses, humans have experienced analgesic and antinociceptive effects, but further increasing the dose of kratom is more likely to produce undesirable gastrointestinal effects, constipation, and lethargy, and little additional mood enhancement.[51]

D. History and Current Pattern of Abuse

Kratom has been used for centuries in Southeast Asia and at least two decades in the United States with little evidence of abuse. In the U.S., people consume kratom almost exclusively in the form of tea brewed from kratom leaves or liquids made from powdered leaves. One study found that the average U.S. customer purchases two to three 2-oz. bottles (doses) per week, and other surveys of U.S. kratom users found typical consumption of one cup of kratom tea per day.[52] Federal surveys have not revealed any instances of people seeking treatment for kratom dependence or addiction.[53] In addition, according to data in the National Forensic Laboratory Information System, kratom is found in only about 0.01% (or one out of every 10,000) reports of drugs seized by authorities.[54] Together, such data indicate little evidence of a public health threat from kratom abuse.

E. Scope, Duration, and Significance of Abuse

Again, there is little, if any, evidence of widespread abuse of kratom in the U.S., as opposed to ordinary and responsible use of a consumer product. The perceived benefits of kratom come with very low risks of serious adverse events, and there is little evidence or apparent risk of use in routes other than oral beverage or food consumption. On internet forums,

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[48] *See* Warner et al., 2016; Neerman MF, Frost RE et al., *A drug fatality involving Kratom*. 58 J. Forensic Sciences S278-79 (2013); Prozialeck WC, Jivan JK, Andurkar SV, *Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects*, 112 J. Am. Osteopathic Ass'n. 792–799 (2012).

[49] *See* Shamima AR, Fakurazi S, Hidayat MT, Hairuszah I, Moklas MA, Arulselvan P, *Antinociceptive Action of Isolated Mitragynine from Mitragyna Speciosa through Activation of Opioid Receptor System*, 13 Int'l J. Molecular Sciences 11427–11442 (2012); Matsumoto K, Hatori Y, Murayama T, Tashima K, Wongseripipatana S, Misawa K, Kitajima M, Takayama H, Horie S, *Involvement of μ-opioid receptors in antinociception and inhibition of gastrointestinal transit induced by 7-hydroxymitragynine, isolated from Thai herbal medicine* Mitragyna speciosa, 549 Euro. J. Pharmacology 63-70 (2006).

[50] *See* European Monitoring Centre for Drugs and Drug Addiction, Kratom (Mitragyna speciosa) drug profile (2015), *available at* http://www.emcdda.europa.eu/publications/drug-profiles/kratom (accessed Nov. 15, 2016) (EMCDDA); Prozialeck, 2012.

[51] *See* EMCDDA, 2015; Prozialeck, 2012.

[52] *See* Henningfield Eight Factor Analysis at 35-37; Henningfield Eight Factor Analysis Appended Testimonials.

[53] *See* Henningfield Eight Factor Analysis at 37-38 (evaluating TEDS data).

[54] *See id.* at 38-40 (evaluating NFLIS data).

frequent drug abusers report little interest in kratom because they are unable to achieve desirable euphoria.[55] Kratom users generally report use for increased alertness and occupational benefits, and to abstain from other substances perceived as addictive or causing harm. Consumers also report mild, unpleasant gastrointestinal effects.

F. The Risk, If Any, to the Public Health

There have been no reports of fatal overdose from kratom per se. All reports in the published literature of deaths involving kratom revealed consumption of other substances known to be respiratory depressants.[56] While there have been three case reports in which kratom may have contributed to the death, there is insufficient evidence to demonstrate kratom's role, if any, in any of these events. Reports to poison control centers involving kratom remain extremely rare, approximately 100-fold more rare than reports involving other uncontrolled substances such as diphenhydramine or aspirin, and about 10-fold more rare than calls involving uncontrolled nicotine smoking cessation products.[57] Remarkably, there has not been a single documented death, serious adverse event, or emergency department admission for a child attributed to kratom exposure.[58] This is likely a function of its low toxicity and low potential for harm, unappealing taste, and low concentration of alkaloids in commercial products. Given the approximately two million kratom consumers in the U.S. alone, kratom has an extraordinarily safe public health profile.

G. Psychic or Physiological Dependence Liability

There have not been adequate studies of physical or psychological dependence or abuse potential in humans caused by kratom. MG has been shown to produce dependence in rats, but at doses equivalent to human consumption of over 1,000 consumer bottles of kratom in a single sitting.[59] Chronic exposure to kratom preparations may be followed by mild symptoms consistent with withdrawal on termination of use, similar to the effects of abruptly abstaining from caffeine after consistent use.[60] The existing research is not completely devoid of signs that could be consistent with abuse or dependence, but neither is there evidence of abuse or dependence potential exceeding that of other unscheduled products that would support the conclusion that CSA scheduling is warranted.

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[55] *See id.* at 41-44 (collecting testimonials from drug abuse website bluelight.org); Swogger et al. (2015) (collecting testimonials from website Erowid.org); Henningfield Eight Factor Analysis at 44-46 (describing survey results from Dr. Oliver Grundmann).

[56] *See* Raffa, 2014, and references cited therein.

[57] *See* Henningfield Eight Factor Analysis at 48 (analyzing AAPCC-NPDS data).

[58] *Id*. at 48-51 (analyzing AAPCC-NPDS data and news reports).

[59] Yusoff NH, Suhaimi FW, Vadivelu RK, Hassan Z, Rümler A, Rotter A, Amato D, Dringenberg HC, Mansor SM, Navaratnam V, Müller CP, *Abuse potential and adverse cognitive effects of mitragynine (kratom)*, 21 Addiction Biology 98-110 (2016).

[60] *See* Suwanlert S, *Study of kratom eaters in Thailand*, 27 Bulletin on Narcotics 21-27 (1975); McWhirter L, Morris S, *A case report of inpatient detoxification after kratom (Mitragyna speciosa) dependence*, 16 Euro. Addiction Research 229-31 (2010).

H. Whether the Substance is an Immediate Precursor of a Controlled Substance

Neither kratom nor any of its constituents or alkaloids is a controlled substance or a precursor of a controlled substance.

The weight of the eight factors counsels strongly against scheduling kratom under the CSA. Kratom's pharmacology predicts low potential for abuse and little risk of respiratory depression, and those effects are borne out in the long history of use of kratom products. The combination of pharmacology and pattern of actual use demonstrate that kratom's abuse potential is consistent with that of other unscheduled substances. In addition, the data show little tendency among kratom consumers to increase their dose to their personal detriment or to the point of addiction, as would indicate a growing dependence. Treatment clinics do not report patients seeking treatment for kratom dependence. Instead, kratom's mild reinforcing effects are unrelated to physical dependence and are consistent with those of a wide range of unscheduled substances. The overall profile of kratom that emerges from the Henningfield Eight Factor Analysis is that of a substance that does not pose a serious risk to the public health and can be effectively regulated under the FDCA, as are other consumer products with comparably low potential for abuse and dependence.

V. USE OF THE EMERGENCY SCHEDULING AUTHORITY TO CONTROL KRATOM IS NOT PERMISSIBLE UNDER THE CSA

In its most recent notice, DEA solicited comments regarding whether the agency should permanently schedule kratom, and whether it should proceed with emergency and permanent scheduling procedures simultaneously.[61] As discussed above, kratom does not satisfy the criteria for permanent placement in any of the schedules. As discussed in more detail in the September 26 Letter, DEA cannot invoke its emergency scheduling authority to control kratom because it does not present an "imminent hazard" to the public safety and it does not meet the requirements for placement in schedule I – particularly, it is not a substance with a high potential for abuse.

Kratom is not the sort of substance contemplated by DEA or Congress when the emergency scheduling provision was created. Kratom has not recently emerged on the illicit market; rather, it is a natural substance that has been consumed in Asia for centuries and has been legally bought and consumed by millions of Americans. The legal and responsible use of kratom by consumers does not constitute abuse. Indeed, as discussed previously, kratom does not provide the kind of euphoria that might render it an appealing drug of abuse and it is not particularly reinforcing. Not surprisingly, then, there is little evidence of historical or current abuse associated with it. Likewise, there is little evidence of a risk to the public health, given the

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[61] 81 Fed. Reg. at 70653.

near absence of serious adverse effects related to kratom and, indeed, the overwhelmingly positive effects on productivity and well-being reported by kratom users. As such, DEA cannot establish an imminent threat to the public health as statutorily required for use of the emergency scheduling process.

Finally, we note that the CSA provides that all substances scheduled through the emergency scheduling process are placed into schedule I. As such, they must meet all of the criteria for placement into that schedule. If the substance fails to meet one of the three findings required for schedule I, it cannot be placed there and, therefore, the emergency scheduling process is not available to DEA. The agency itself has acknowledged this important statutory principle. As reflected by the Supreme Court in *Touby v. United States*:

> In addition to satisfying the numerous requirements of 201(h) [regarding emergency scheduling], the Attorney General must satisfy the requirements of 202(b), 21 U.S.C. 812(b). This section identifies the criteria for adding a substance to each of the five schedules. *As the United States acknowledges in its brief,* 202(b) speaks in mandatory terms, drawing no distinction between permanent and temporary scheduling. With exceptions not pertinent here, it states that "a drug or other substance may not be placed in any schedule unless the findings required for such schedule are made with respect to such drug or other substance." *Thus, apart from the "imminent hazard" determination required by 201(h), the Attorney General, if he wishes to add temporarily a drug to schedule I, must find that it "has a high potential for abuse," that it "has no currently accepted medical use in treatment in the United States," and that "[t]here is a lack of accepted safety for use of the drug . . . under medical supervision."*[62]

Thus, as a matter of law, because kratom does not meet the criteria for placement in schedule I – in particular, it is not a drug with "a high potential for abuse" – it cannot be scheduled via the expedited process, even independent of the "imminent hazard" inquiry.[63]

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[62] 500 U.S. 160, 166-67 (1991) (citations omitted) (emphasis added). *See also* DEA's Notice of Intent to temporarily place mitragynine and 7-hydroxymitragynine into schedule I, 81 FR at 59930 ("A substance meeting the statutory requirements for temporary scheduling may only be placed in schedule I. Substances in schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.") (citations omitted).

[63] In addition, use of the emergency scheduling provision to control kratom may violate fundamental principles of regulatory procedure and raise serious questions of constitutional law. These issues were described in detail in the attached September 26 Letter.

VI. POLICY CONSIDERATIONS WEIGH STRONGLY AGAINST SCHEDULING KRATOM

Substances are not scheduled in a vacuum. Beyond the technical application of the statutory criteria, the scheduling of kratom would have diverse and significant real-world costs. First, the administrative scheduling process itself, having been designed as a deliberate, comprehensive governmental exercise, is lengthy and resource-intensive. After scheduling, more governmental resources would be necessary to enforce the statute, which would necessarily be diverted from efforts related to far more dangerous substances. Meanwhile, the cost to the public would be considerable, especially on those Americans who would be denied access to a product they had been safely and responsibly consuming for years. Immigrants from Southeast Asia and their families, who brought with them the custom of consuming kratom as a regular part of their lives, would be particularly harmed. Likewise, the small businesses across the country that have been involved in the sale and distribution of kratom products would be irrevocably harmed. What's more, it can be expected that some long-term kratom consumers would turn to the illicit market, facing the risk of arrest and criminal sanctions, and risking their health with unregulated products that may be mislabeled and adulterated.

Contrast these costs of scheduling kratom with the tenuous benefits. As discussed in this letter and the attachments, kratom has a low potential for abuse – as low, or lower, than that of other unscheduled substances. Accordingly, the typical hallmarks of abuse are absent in real-world experience: few or no overdoses of kratom, and few reports of kratom being used to attain euphoria – an effect that would be difficult to achieve, given the substance's low bioavailability and mitigating antagonist activity. Likewise, its effects are mild and kratom seems to cause little or no dependence, as evidenced by virtually no demand for substance abuse treatment programs for kratom use. The botanical substance has demonstrated a long and remarkable safety profile, with no reported deaths or serious adverse events caused solely by kratom and no documented serious adverse events in children. Kratom simply does not present a significant danger to the public health, and certainly not a crisis of the sort to justify the extraordinary costs of scheduling a substance. This is especially true when the substance in question has a long history of safe use in this country and abroad. Furthermore, many consumers choose to use kratom on their own volition as a natural remedy or to help them abstain from or reduce the use of other substances perceived as addictive or causing harm, such as opioids, benzodiazepines, and antidepressants.[64] As a result, these consumers avoid substances with far greater toxicity, dependence liability, and potential for abuse by taking kratom. For these reasons, Dr. Henningfield concluded that the scheduling of kratom would be "more likely to cause public health problems that do not presently exist" than to solve an existing public health crisis.[65]

VII. THE FDCA PROVIDES THE APPROPRIATE REGULATORY SCHEME FOR KRATOM PRODUCTS

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[64] Henningfield Eight Factor Analysis at 19, 43-44.

[65] *Id*. at 16.

While kratom does not meet the criteria for scheduling under CSA, there are other mechanisms for exerting appropriate control over kratom products. FDA may continue to regulate these products through its authority in the FDCA and implementing regulations. For example, FDA has the authority to ensure that labeling of kratom products is not false or misleading.[66] This includes the requirement to accurately identify the product and any additional ingredients and to not misrepresent the MG or 7-OH-MG content of the product. FDA can also regulate misbranding of the product through claims made in labeling, including promotional advertising.[67] Moreover, states may also take steps to regulate kratom; some states have already set a minimum age to purchase or consume kratom, and others are studying the substance to guide future policy.

Such oversight of kratom would be comparable to the regulation of similar products – and even those that are, arguably, more similar to drugs of abuse. For example, the botanical substances St. John's Wort, Valerian, and Kava Kava are known to have reinforcing effects and to act as sedatives, and have been the subject of hundreds or thousands of calls to Poison Control Centers. Yet, these substances have not been scheduled, but have been regulated as dietary supplements. The same is true for guarana and kola nut, which also have certain characteristics of a drug of abuse. Yohimbine, the primary component of yohimbe extract, is an indole-containing alkaloid that is structurally similar to mitragynine, yet yohimbe is available in the U.S. as a dietary supplement. Numerous other examples of unscheduled botanical substances with some reinforcing effects exist, including Passionflower, Ashwagandha, Schisandra, California Poppy, Lemon Balm, Red Clover, Catnip, Motherwort, Skullcap, and poppy seeds. None of these botanical substances is scheduled, despite sharing some characteristics with controlled substances; rather, all of them are adequately regulated by FDA through existing authority. Kratom, with a comparable or lower potential for abuse than these substances, would likewise be best regulated under the FDCA.

VIII. CONCLUSION

Kratom is a natural botanical product consumed by millions of Americans daily. Like caffeine, when used responsibly, kratom is enjoyable, safe, rarely associated with any serious adverse effects, and not prone to abuse. Kratom simply does not pose an imminent threat to the public health. Nor does it share fundamental characteristics with substances controlled in schedules II-V. Rather, kratom is more reasonably characterized as a dietary supplement, and could be ably regulated as such by FDA. Through that regulatory framework, manufacturers and distributors of kratom could be held accountable for the safety and labeling of their products, while ensuring continued access to Americans who consume them. We believe such an approach would represent a much more efficient use of governmental resources than the scheduling process could provide.

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[66] 21 U.S.C. § 343.

[67] *See id.* at §§ 352, 355.

Thank you for your time and consideration of this important matter.

Sincerely,

Lynn Mehler

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Congress of the United States
Washington, DC 20515

September 30, 2016

Honorable Loretta E. Lynch
Attorney General
U.S. Department of Justice
950 Pennsylvania Avenue, NW
Washington, DC 20530-0001

Dear Attorney General Lynch,

We are writing to object to DEA's hasty decision to classify the drug known as Kratom as a Schedule I substance. In particular, we are troubled by the DEA's irregular deviation from its classification procedure in order to list Kratom as a Schedule I substance. We call on you to stay the effective date of this proposed rule.

In order to schedule a drug, the DEA must undertake a rulemaking process, which involves consultation with the FDA, notice of the proposed rule in the Federal Register, and an opportunity for public comment and a hearing. Under this standard process, DEA must consider eight factors as part of its analysis, as listed in 21 U.S.C. § 811(c). However, in its decision to classify Kratom as a Schedule I substance, DEA instead utilized a statutory authority to temporarily bypass the rulemaking process as well as the notice and public comment period. However, under 5 U.S.C. § 705, an agency may postpone the effective date of an action when justice requires it. As the head of the Department of Justice, which oversees the DEA, we ask you to stay the effective date of this rule, so that the appropriate notice and public comment period may take place.

Congress granted DEA this authority in response to the emergence of "designer drugs." Designer drugs are those newly invented or newly produced in laboratories and are designed to mimic the effects of scheduled substances while avoiding federal regulation. Kratom, though relatively new to the United States, does not fit this description. It is a natural substance that has been used in other parts of the world for centuries.

Furthermore, Congress granted DEA this emergency authority "to avoid imminent hazards to public safety." While a recent CDC study does note the number of calls to poison control centers mentioning Kratom use has increased, the data does not indicate that Kratom was solely responsible for the calls. Without more concrete data and analysis, it is difficult to claim Kratom represents an "imminent hazard." Access to improved data and further studies will now be impossible to gather should Kratom be scheduled as Schedule I substance.

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We appreciate the DEA's desire to protect Americans from potentially harmful substances. However, in this case DEA has overstepped its authority in a manner that is inconsistent with the intent of the statutory authority it was given by Congress. In effect, the DEA removed any opportunity for the agency to be held accountable for its decision making. If the DEA believes that Kratom is of notable detriment to Americans and wishes for it to be scheduled, it should follow normal procedure and rigorously defend its views to Congress, the FDA and the public. It is for these reasons you should stay the effective date of rule and allow for the appropriate notice and comment period to take place.

We thank you for your consideration and look forward to your timely response.

Sincerely,

Henry C. "Hank" Johnson, Jr.
Member of Congress

Mark Pocan
Member of Congress

CORY A. BOOKER
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United States Senate

September 29, 2016

VIA ELECTRONIC TRANSMISSION
The Honorable Charles P. Rosenberg
Acting Administrator
U.S. Drug Enforcement Administration
8701 Morrissette Drive
Springfield, VA 22152

Dear Acting Administrator Rosenberg:

We write with concern about your agency's proposed regulatory action to place mitragynine and 7-hyroxymitagynine, key constituents of the kratom plant, into Schedule I of the Controlled Substances Act (CSA) without undertaking a robust process of stakeholder input and discussion of medical, public safety, and scientific considerations. Specifically, we would like the Drug Enforcement Administration (DEA) to delay its scheduling decision on kratom, and extend the public comment period for stakeholders to weigh in on this proposed regulatory action.

On August 31, 2016, the DEA posted notice in the Federal Register that it was going to place kratom into Schedule I within 30 days. We are concerned that the 30-day comment period for such a proposed regulatory action is not a sufficient amount of time for public comment on a drug that, according to recent scientific studies, may actually be an effective substance to help combat the opioid epidemic. While we understand there are times when public safety demands that your agency act quickly on scheduling decisions, we believe that in this instance additional time for the scientific community, public health officials, and other members of the public to comment is warranted and may prove to be in the interest of public health and safety.

As you know, Schedule I of the CSA is reserved for substances that have a high potential for abuse and that have no currently accepted medical use. An increasing body of research has shown kratom's potential value as a treatment for a number of conditions. On September 2, 2016, eleven scientists from well-respected research institutions in the U.S. wrote an open letter to Congress expressing "grave concern" about the agency's proposed action and expressed their opposition to any efforts to designate kratom as a Schedule I controlled substance of the CSA.[1] In their letter, the scientists wrote:

> [T]here are a significant number of individuals using kratom as a treatment for numerous medical conditions, including chronic pain, depression, and weaning addictions to other, more dangerous opioids. Although instances of self-medication are concerning to us in the medical community, the majority of such patients so far report that they achieve therapeutic benefits with few side effects, while occurrences of serious abuse or dependence remain infrequent.

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[1] Letter attached from Andrew C. Kruegel, PhD, et al., to Congress (Sept. 2, 2016).

Given that we are in the midst of a drug crisis and there is promising evidence of kratom's potential medical benefits, including the possibility of new, safer medications for the treatment of pain, we believe that placing kratom in Schedule I without adequate time for experts to weigh in via public comment may have unintended consequences.

Furthermore, since 1980, our federal prison population has exploded by nearly 800 percent. This increase is a result of draconian drug policies that continue to place nonviolent drug offenders behind bars. We should not, in haste and without adequate opportunity for comment and analysis, place substances in categories that may be inconsistent with their medical value and potential for abuse.

We believe that your agency can more fully engage consumers, researchers, and other stakeholders in the well-established protocol for significant matters such as this one. Thank you for your prompt attention.

Sincerely,

Cory A. Booker
United States Senator

Kirsten Gillibrand

Kirsten E. Gillibrand
United States Senator

Ron Wyden

Ron Wyden
United States Senator

September 2nd, 2016

We are writing to express the grave concern of some of us in the scientific community regarding the just-announced Drug Enforcement Administration proposal to place key constituents of the kratom plant, mitragynine and 7-hydroxymitragynine, into Schedule 1 of the Controlled Substances Act. Our laboratories at Columbia University, Memorial Sloan Kettering Cancer Center, and partner institutions are currently engaged in extensive research efforts involving these natural compounds, their synthetic analogs, and other opioid modulators, which we feel will be jeopardized by a prohibition. We seek to understand the actions of this unique molecular class in both cells and animals, and to better evaluate its potential as a starting point for developing new medications. Ultimately, we believe mitragynine analogs may serve as new painkillers that eliminate many of the dangers associated with those opioid analgesics in current use (e.g. morphine and oxycodone).

Research in cells and animals, both in our laboratories and those of others, is consistent with an enhanced safety profile for mitragynine and its analogs. Due to unique properties of their molecular signaling (Kruegel *et al. JACS*, 2016) in the brain, several compounds in this class are effective pain relievers but induce limited respiratory depression in animals; an important point considering that respiratory failure is the key cause of death from opioid overdose. Another semi-synthetic analog in this series also exhibits greatly attenuated tolerance, dependence, and abuse potential in animal models (Váradi *et al. J Med Chem*, 2016). Further, a synthetic drug with similar molecular signaling properties, oliceridine (TRV130), is currently in Phase 3 clinical development and has demonstrated improved respiratory safety in humans, thus exemplifying the clinical potential of mitragynine analogs. **The kratom alkaloids therefore represent a major and unique opportunity to address the opioid crisis that is currently sweeping our nation, through the development of new, safer drugs for pain.**

Hundreds of years of human use worldwide further suggest, albeit in an anecdotal manner, that kratom is typically safe, with no substantiated fatal overdoses from kratom plant consumption alone (in contrast to >18,000 deaths per year from prescription opioids and >10,000 from heroin). In fact, there are a significant number of individuals using kratom as a treatment for numerous medical conditions, including chronic pain, depression, and weaning addictions to other, more dangerous opioids. Although instances of self-medication are concerning to us in the medical community, the majority of such patients so far report that they achieve therapeutic benefits with few side effects, while occurrences of serious abuse or dependence remain infrequent.

In sum, we are strongly opposed to any scheduling efforts directed towards the control of kratom or its molecular constituents at the present time. Although the availability of novel opioid modulators certainly represents a point of concern, there is currently no strong evidence to suggest that kratom use poses a major threat to public health or safety. In fact, the available data instead speaks to a favorable safety profile compared to other drugs in the opioid class. Furthermore, much more research is needed to establish any potential risks associated with use of kratom by the public and to evaluate the medicinal potential of mitragynine and its analogs; work which will be challenging in a prohibition environment. **Placing these compounds into Schedule 1 will erect an enormous barrier to scientific research in this field and will dramatically curtail our work with this exciting plant. Thus, an outright ban of kratom is not the scientific choice at present.**

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United States Senate
WASHINGTON, DC 20510

September 30, 2016

The Honorable Charles P. Rosenberg
Administrator (Acting)
Drug Enforcement Administration
Lincoln Place-West
700 Army Navy Drive
Arlington, VA 22202

Dear Acting Administrator Rosenberg:

We write today in regards to the Drug Enforcement Administration (DEA) Notice of Intent Docket No. DEA 442, the Temporary Placement of Mitragynine and 7-Hydroxymitragynine (commonly known as "Kratom") into Schedule I. This Notice provides the Senate an opportunity to review the current DEA practices and gather additional information on how evidence is selected for scheduling decisions.

The standard required for triggering the emergency scheduling authority under the Controlled Substances Act (CSA)[1] requires an immediate threat to the public safety based on a public record of injuries or deaths caused by the substance being recommended for scheduling. Congress granted emergency scheduling authority to the DEA based on the need for law enforcement interdiction of new and previously unknown illegal synthetic street drugs that result in injuries and death. The use of this emergency authority for a natural substance is unprecedented, so it is important to determine whether the circumstances here necessitate a jump to Schedule I.

Congress has established a specific set of review protocols for scheduling decisions that will create significant disruption in the marketplace that allows for the full engagement of consumers, researchers, health professionals, law enforcement officials, and other stakeholders. Given the long reported history of Kratom use, coupled with the public's sentiment that it is a safe alternative to prescription opioids, we believe using the regular review process would provide for a much-needed discussion among all stakeholders. We understand the DEA's desire to uphold public health and safety, and we share the goal of seeing unsafe products removed from the market. However, hearing multiple perspectives allows for more fulsome decision-making.

Given the extremely short timeframe for the implementation of the proposed DEA scheduling order, we urge you to take appropriate steps to delay the order to allow both for a public

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[1] Section 201(h)(4); 21 U.S.C. 811(h)(4).

comment period and sufficient time for the DEA to outline its evidentiary standards to Congress regarding the justification for this proposed action.

Sincerely,

Orrin Hatch

Orrin G. Hatch
United States Senator

Michael F. Bennet
United States Senator

Angus King

Angus S. King, Jr.
United States Senator

Mark Kirk
United States Senator

Mike Lee
United States Senator

Bernard Sanders
United States Senator

Thom Tillis

Thom Tillis
United States Senator

Mark R Warner

Mark R. Warner
United States Senator

Ron Wyden

Ron Wyden
United States Senator

IPSynergy
for the Life Sciences

Jane K. Babin, Ph.D., Esq.
Attorney-at-Law
Registered Patent Attorney
Ph.D. Molecular Biology

December 1, 2016

Michael J. Lewis
Office of Diversion Control
Drug Enforcement Administration
Attn: DEA Federal Register Representative
8701 Morrissette Drive
Springfield VA 22152-1080

Re: Docket No. DEA-442W

Dear Mr. Lewis:

I am writing to urge the Drug Enforcement Administration (DEA) to terminate efforts to schedule mitragynine (MG) and 7-hydroxymitragynine (7-OH-MG), constituents of the Kratom plant (*Mitragyna speciosa*), pursuant to either the emergency[1] or regular[2] scheduling provisions of the Controlled Substances Act (CSA)[3], pending definitive scientific analysis of the risks and more importantly the benefits of Kratom and its constituent alkaloids. It is my opinion that the benefits of Kratom vastly outweigh any risks.

The DEA initially proposed temporarily placing MG and 7-OH-MG under Schedule I of the CSA, along with such hallucinogenic substances as LSD, psilocybin, mescaline, and highly addictive opioids such as heroin, because it concluded that such action was "necessary to avoid an imminent hazard to the public safety" [4]. This conclusion was premature and appears to have been made based on contradictory opinions, incomplete knowledge of the most current scientific evidence and without input from the public on their experiences with Kratom[5]. I applaud the DEA for withdrawing its intent to temporarily place mitragynine and 7-hydroxymitragynine in Schedule I and instead soliciting comments from the public.[6] I am confident that after considering the pertinent scientific facts, particularly recent evidence distinguishing MG and 7-OH-MG from scheduled opioids, and the overwhelmingly positive experiences of Kratom users as evidenced by more than 20,000 comments reflecting the views of current Kratom users, the DEA will conclude that scheduling these compounds is neither necessary nor in the public interest.

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[1] 21 U.S.C. §811(h).

[2] 21 U.S.C. §811(a)-(c).

[3] 21 U.S.C. §801et seq.

[4] 81 FR 59929, at 59929, col. 1.

[5] Gosa, "Kratom ban withdrawn by DEA. DEA admits conflicting information about Kratom," Albany Herald, Oct 27, 2016 (Quoting DEA spokesperson Melvin Patterson: "We received some conflicting information in regards to the effect of Kratom. We had a specialist and there was an outside specialist, but they had conflicting information on how Kratom affected the Mu receptors in the brain. So we decided to step back, take public comment and do this the right way, get as much information (as possible) before going forward.")

I trust that the DEA will objectively evaluate all the input and evidence presented herein, and by others, when reaching its decision, rather than repeat the mistake of rushing to judgment based on inappropriate generalizations and unsupported or hysterical tirades from those who may have ulterior motives for their opinions as the Centers for Disease Control (CDC) did when issuing opioid prescribing guidelines. The DEA's action on this issue can pave the way to a future in which the often conflicting interests of individuals with substance abuse disorders, mental illnesses, chronic and acute pain converge on solutions to the problems facing all members of our society, rather than pitting one group against the other. Based on the evidence available today, it is reasonable to conclude that Kratom may provide these solutions.

Eight-Factor Analysis under the CSA

Dr. Jack Henningfield of PineyAssociates has prepared an extensive evaluation of Kratom under the CSA[7], submitted as an attachment to the comments of the American Kratom Association[8]. I have reviewed and endorse these documents wholeheartedly. In the interest of avoiding duplication, Dr. Henningfield's analysis and the AKA Comments are incorporated herein by reference in their entirety.

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[6] 81 FR 70652,

[7] Henningfield, "Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation", November 28, 2016, pp. 1-128, submitted on Regulations.gov, Docket No. DEA-442W, on behalf of the American Kratom Association; see http://www.prnewswire.com/news-releases/american-Kratom-association-major-new-analysis-shows-no-basis-for-dea-to-restrict-herb-Kratom-300371521.html.

[8] Mehler & Fox, "Mitragynine and 7-Hydroxymitragynine, Constituents of the Kratom Plant, Should Not Be Scheduled under the Controlled Substances Act", November 30, 2016, pp. 1-17, submitted on Regulations.gov, Docket No. DEA-442W on behalf of the American Kratom Association; hereinafter "AKA Comments"; *see id.*

My further comments expand on specific issues that I believe are critical to a complete understanding of Kratom.

Kratom versus Mitragynine and 7-hydroxymitragynine

At the onset, it is important to distinguish the difference between Kratom (the plant, *Mitragyna speciosa*) and constituent alkaloid components MG and 7-OH-MG that make up only a small fraction of the dry weight of the plant leaves. A blanket ban on MG and 7-OH-MG (the compounds), would necessarily be a ban on Kratom (the plant material), while a ban on Kratom would not necessarily be a ban on MG and 7-OH-MG.

Much of the concern surrounding Kratom is based on the effects of isolated and purified MG and 7-OH-MG. Yet the DEA has provided no evidence that purified, pharmaceutical grade MG and/or 7-OH-MG is available to consumers; the only demonstrated uses of such purified compounds has been in the context of research and in extraordinary amounts. As isolated compounds, MG and 7-OH-MG have properties that hint at the effects of Kratom when consumed as a botanical supplement. Yet the compounds in isolation cannot approach the complexities of Kratom when consumed as a dietary supplement. While concerns surrounding the heterogeneity, variability and purity of Kratom are often cited as reasons for scheduling it, such concerns are not limited to Kratom and are more appropriately addressed by other provisions of the FDCA that protect consumers from adulterated, misbranded and contaminated food and dietary supplements.

Kratom is Not a "Drug" and is Neither "Abused" nor "Misused"

One indication of the DEA's past prejudicial evaluation of kratom is evidenced by the characterization of Kratom consumption as "abuse" and "misuse". These pejorative terms beg the question of whether the DEA had already resolved to schedule kratom based on a knee-jerk reaction to studies showing that MG and 7-OH-MG bind to opioid receptors. Such a reaction presumes that simply because the compounds bind opioid receptors they must inherently be addictive drugs, and since they have not been approved by the FDA under a New Drug Application (NDA) or a Biologics License

Application (BLA), they must be abused or misused rather than simply consumed as integral components of the herbal supplement, Kratom.

Under the Federal Food Drug and Cosmetic Act (FDCA)[9], a "drug" is not defined structurally, chemically or biologically, but by its recognized listing in one of a limited number of compendia or more often by its intended use.[10] Thus, a proteolytic preparation sold as a meat tenderizer is not a drug, but when sold as a treatment for epidural injection for treatment of degenerative disc disease, it is a drug.

While it has been suggested that Kratom is used for certain purposes, DEA has provided no proof that Kratom, MG and 7-OH-MG are marketed as drugs intended for use in the diagnosis cure, mitigation, treatment, or prevention of disease in man or other animals.

The Dietary Supplement Health and Education Act of 1994 (DSHEA)[11] contemplates the fact that dietary supplements may have physiological and pharmacological effects, but recognizes the autonomy of individuals to make choices regarding their own health based on their own studied evaluations of specific dietary supplements, including herbal products. At the time of enactment of the DSHEA, a majority of Americans reported consuming one or more dietary supplements, and Congress recognized the significance Americans place on having such products and accurate information on

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[9] United States Code, Title 21.

[10] 21 U.S.C. §321(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

[11] P.L. 103-417.

their effects available.[12] Such products then included substances that may have physiological and pharmacological properties, which did not then, and does not now render dietary supplements "drugs" under the FDCA.

"Abuse" is defined only once in the FDCA, as:

> (A) the illegal use or abuse of drugs, including substances listed in schedules I through V of section 812 of this title;
> (B) the abuse of inhalants; or
> (C) the use of alcohol, tobacco, or other related product as such use is prohibited by State or local law.[13]

Thus, only inhalants and ***illegal*** substances are appropriately deemed "abused" under the FDCA.

Kratom, MG and 7-OH-MG are banned or restricted in certain State and/or local jurisdictions, but are not illegal under federal law.[14] Therefore, characterization of use of Kratom by DEA as "abuse" is inappropriate and presumptive of a scheduling determination that has not yet been made.

Context of Proposed Scheduling – The Opioid Epidemic.

The proposal to schedule MG and 7-OH-MG comes on the heels of a crisis in opioid abuse and overdoses, characterized by CDC as an "epidemic"[15]. According to CDC, "the number of overdose deaths involving opioids (including prescription opioid pain relievers and heroin) nearly quadrupled" between 1999 and 2014[16]. Indeed, the numbers of deaths from opioids is quite high: in 2014 there were almost 19,000 deaths

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[12] Commission on Dietary Supplement Labels, Final Report Transmitted November 24, 1997, viewed at https://health.gov/dietsupp/default.htm.

[13] 21 U.S. Code § 1523

[14] *See* Henningfield, *infra*.

[15] *See e.g.*, "Understanding the Epidemic", http://www.cdc.gov/drugoverdose/epidemic/index.html, viewed December 1, 2016.

[16] *Id. citing* "CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov.

involving prescription opioids[17] and 10,500 deaths attributed to heroin[18]. According to the Substance Abuse and Mental Health Services Administration there are "an estimated 2.1 million people in the United States suffering from substance use disorders related to prescription opioid pain relievers in 2012 and an estimated 467,000 addicted to heroin."[19] Thus, roughly 2.5 million people are addicted to heroin and opioid pain relievers, resulting in roughly 30,000 deaths per year.

There is no question that opioid addiction and mortality is a problem, but the solution is less clear.

The zealots in the addiction treatment industry have apparently hypnotized otherwise intelligent individuals into believing that the only way to save victims of opioid addiction is to acquiesce to the fiction they espouse: that a life of pain for 100 million patients is more acceptable than the risk of addiction of perhaps 2.5% of those patients, and the otherwise inevitable overdose deaths of 1.2% of those addicts. They convinced the CDC to issue "voluntary guidelines" for "safer" opioid prescribing using data compiled and analyzed according to the "Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method."[20] The "Guideline" was widely criticized for providing strong recommendations based on weak evidence, supplemented with input from a secret panel of "experts" heavily biased toward addiction treatment (typically medication assisted treatment, which may be little more than medically-sanctioned addiction) and against opioids.[21] There is nothing safer

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[17] *See* http://www.cdc.gov/drugoverdose/data/analysis.html, viewed December 1, 2016.

[18] *See* http://www.cdc.gov/drugoverdose/data/heroin.html, viewed December 1, 2016.

[19] *See* https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse (viewed December 1, 2016), citing Substance Abuse and Mental Health Services Administration, *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.

[20] *See* http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm, viewed December 1, 2016.

[21] *See e.g.*, Letter from Jordan-Meadows-Cartwright-Connolly-to-Frieden-CDC-FACA, December 18, 2015-due-Jan.-5; Videocast and transcript from the Interagency Pain Research Coordinating Committee (IPRCC), December 5. 2015available at https://videocast.nih.gov/summary.asp?Live=17523&bhcp=1 (in which, *inter alia*, one member of the committee members describes the guidelines as an "embarrassment" to the government); Anson, "Congress Investigating CDC's Opioid Guidelines", Pain News Network, December 22, 2015,

about the CDC Guideline. It simply exchanges one harm for another, leading many chronic pain patients to choose between a life of pain, a life of crime purchasing pain medications on the black market and suicide.

They have gone so far as to suggest that we should no longer even ask patients about their level of pain.[22] Jayne Ballantyne's paper in the New England Journal of Medicine espouses a psycho-babble excuses for avoiding treatment of pain: "[s]uffering may be related as much to the meaning of pain as to its intensity"; over time "pain intensity becomes linked less with nociception and more with emotional and psychosocial factors'; and that a biopsychosocial approach to pain (in lieu of actual medical treatment) having a goal of "acceptance" "might make the intensity of pain less important to a person's functioning and quality of life."[23] I call this what it is – B.S. Anyone who has suffered actual physical pain will appreciate that no amount of consoling, distraction, discussion, reasoning, or counseling will lessen the absolute physical burden it imposes.

Yet this and similar arguments have been remarkably effective with those who merely want to ***gain the appearance of doing something***. For example, such arguments have convinced Medicaid to remove questions about pain from hospital satisfaction questionnaires given to patients.[24] Specifically, three questions are being dropped in 2017:

1. During this hospital stay, did you need medicine for pain?
2. During this hospital stay, how often was your pain well controlled?
3. During this hospital stay, how often did the hospital staff do everything they could to help you with your pain?

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https://www.painnewsnetwork.org/stories/2015/12/21/congress-investigating-cdcs-opioid-guidelines?rq=opioid%20guideline, and many others.

[22] Ballantyne & Sullivan, "Intensity of Chronic Pain — The Wrong Metric?", New England J. Med. 373:2098-2099, 2015

[23] *Id.*

[24] Anson, "Medicare Pain Questions Being Dropped in 2017", Pain News Network, November 3, 2016, viewed at https://www.painnewsnetwork.org/stories/2016/11/3/medicare-pain-questions-dropped-in-2017.

In making this change, the Centers for Medicare and Medicaid Services stated "[w]hile there is no empirical evidence of such an effect, we are finalizing the removal of the pain management dimension of the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) Survey…to eliminate any financial pressure clinicians may feel to overprescribe medications."[25] So the anti-pain lobby has not only suppressed pain treatment, but has actually wiped any discussion of pain treatment off the map, with a don't ask, don't tell mentality, as though pretending pain doesn't exist will make it go away.

The anti-pain, anti-opioid camp has further justified their rhetoric by exaggerating the infrequent side effect of opioid-induced hyperalgesia[26]. The CDC first concluded that there is no evidence that opioids are effective in chronic pain[27], but rather than recommend further study as the Agency for Healthcare Research and Quality (AHRQ) did[28], CDC recommended against opioid use by interpreting absence of evidence to be evidence of absence of efficacy. The perversion of the AHRQ report has become a mantra for the anti-pain lobby often stated as: "we now know that opioids are not effective for chronic pain…"

The zealots were wrong on all counts.

Restriction of opioids **has not** had the effect of lowering opioid deaths, as evidenced by a recent report from the Massachusetts Department of Public Health indicating that opioid deaths have ***increased substantially*** since the release of the CDC Guidelines, attributable to opioids previously characterized as "prescription drugs", but now

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[25] *Id.*

[26] Opioid induced hyperalgesia is the paradoxical effect of increasing pain with increasing opioids. OIH is distinguish from tolerance in that in tolerance pain can be overcome by an increase in opioid dose, while an in opioid dose increases pain in OIH; see e.g. Tompkins & Campbell, "Opioid-Induced Hyperalgesia: Clinically Relevant or Extraneous Research Phenomenon?" Curr Pain Headache Rep. 15: 129-136,.

[27] *See* http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm, viewed December 1, 2016.

[28] Chou *et al.* "The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain" AHRQ Publication No. 14-E005-EF, September 29, 2014, viewed at *https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1988.*

recognized as counterfeit fentanyl and analogs thereof.[29] Indeed, the DEA's own reports support this observation.[30] Of even greater concern is the fact that even more dangerous counterfeit opioids have been appearing in the illicit drug supply, including carfentanil, a drug that the DEA describes as "10,000 times more potent than morphine and 100 times more potent than fentanyl".[31] There's nothing safer about the current government approach to opioids. While the supply of pharmaceutical opioids manufactured under GMP conditions available for diversion may have diminished, much more dangerous counterfeit replacements have followed in lock-step.

Increasingly, physicians and others are speaking out against the heavy-handed, supply side approach advocated by the anti-opioid lobby, and calling out the CDC for relying on "faulty data and [failing] to address the changing nature of opioid abuse when it released its opioid prescribing guidelines in March [2016]. Since then, many pain patients have reported their opioid doses have been lowered or discontinued, while some have been discharged by their physicians and forced to seek treatment elsewhere."[32] According to Stefan Kertesz, MD, an associate professor at the University of Alabama at Birmingham School of Medicine "[r]educing opioid prescribing is not going to save many lives at this point, even though it gives many officials ***a chance to look like they are doing something.***"[33]

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[29] *See* Massachusetts Department of Public Health, "Data Brief: Opioid-related Overdose Deaths Among Massachusetts Residents," November 2016, viewed at http://www.mass.gov/eohhs/docs/dph/stop-addiction/current-statistics/data-brief-overdose-deaths-nov-2016-ma-residents.pdf.

[30] "Counterfeit Prescription Pills Containing Fentanyls: A Global Threat", DEA-DCT-DIB-021-16, July 2016, viewed at https://www.dea.gov/docs/Counterfeit%20Prescription%20Pills.pdf.

[31] "DEA Issues Carfentanil Warning to Police and Public", September 22, 2016, viewed at https://www.dea.gov/divisions/hq/2016/hq092216.shtml;Healy, "Drug Linked to Ohio Overdoses Can Kill in Doses Smaller than a Snowflake," New York Times, September 5, 2016 viewed at http://www.nytimes.com/2016/09/06/us/ohio-cincinnati-overdoses-carfentanil-heroin.html?_r=0; Mettler, "This is unprecedented': 174 heroin overdoses in 6 days in Cincinnati," Washington Post, August 29, 2016, viewed at https://www.washingtonpost.com/news/morning-mix/wp/2016/08/29/this-is-unprecedented-174-heroin-overdoses-in-6-days-in-cincinnati/?utm_term=.4aca1c0a9dfb.

[32] Anson, "Fentanyl & Heroin Changing U.S. Opioid Epidemic, Pain News Network, November 19, 2016 viewed at https://www.painnewsnetwork.org/stories/2016/11/19/fentanyl-heroin-changing-us-opioid-epidemic;

[33] *Id.* (emphasis added).

Indeed, pain patients have been abandoned by their physicians, abruptly cut off from pain medications, and left to their own devices for relief. Some have committed suicide. Those that are still able to obtain pain treatment are subjected to inconvenience of visiting their physicians at least monthly, involuntary titration of their medication, humiliation, accusations of addiction and drug-seeking behavior, restrictive and derogatory pain contracts, urine drug screening, pill counts and more.

Those that are able to find pain treatment are funneled into the offices of an increasingly small number of pain clinics and physicians. Those practitioners brave enough to continue prescribing opioid pain medication in the face of increasing scrutiny by medical boards, local law enforcement and particularly the DEA, are operating at maximum capacity, and seeing increasing numbers of patients as the availability of care dwindles. Rather than support these highly trained professionals operating under stressful conditions, the DEA targets them because they are now prescribing above-average numbers of opioids.

Under these circumstances, why would a pain patient not seek relief outside of conventional medical care that has obviously lost its way? I would.

A turning point for me was when I read recommendations from the American Pain Society seeking the next step ***beyond*** the CDC Guideline for Chronic Pain, by suggesting that epidural anesthesia was appropriate for major thoracic surgery (e.g., thoracotomy). I visualized my daughter, who has had three open heart surgeries (at ages 3 months, 18 months and 10 years), screaming as she watched the cardiovascular surgeon approach with a rib-spreader. While this may not be what was intended, at what point do we as a reasonable American public tell the government that ***merely looking like it is doing something***, whether it is the right thing to do or not, is simply not acceptable?

I CALL ON THE CDC TO GO BEYOND

MERELY LOOKING LIKE IT IS DOING SOMETHING:

IT IS TIME TO DO THE RIGHT THING!

Why is Kratom Important?

Kratom may be a better way; perhaps the best way available in the current medical reality.

The tens of thousands of Kratom users who have commented on Regulations.gov attest to the safety and efficacy of Kratom in addressing analgesia, depression and opioid addiction. The sheer volume of comments from living, breathing adults clearly indicates that Kratom is less harmful than either scheduled or illicit opioids. The overwhelming majority of the now 20,000+ comments (and I have read a substantial number of them) are from Kratom users who oppose scheduling. If the rate of deaths amongst just these Kratom users alone was the same as those that abuse scheduled and illicit opioids, there should be 240 deaths per year among them[34]. If there are, as the American Kratom Association estimates, between 2 and 5 million regular kratom users, and all of these are "abusers" of a "drug" as dangerous as heroin and prescription opioids (as the DEA suggests), then we would expect on the order of 24,000 to 60,000 deaths per year. Even if only 2.5% were "addicts" (as is the percentage of opioid users who are addicts, according to the CDC), there would be hundreds or thousands of deaths per year instead of the one (1) that could not be accounted for by polypharmacy in five years.

The few that have experienced negative side effects ***while coincidentally*** using Kratom (not because of using Kratom), have generally used unimaginably excessive amounts of Kratom or have co-ingested other harmful substances. [35]

For example, the individual reported by Boyer et al. in 2008[36] was spending $15,000 a year on Kratom. He didn't experience adverse effects for 3.5 years before have a seizure

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[34] 30,000 deaths per 2,500,000 opioid and heroin addicts = 12 per thousand.

[35] Henningfield, "Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation", November 28, 2016, pp. 1-128, submitted on Regulations.gov, Docket No. DEA-442W, on behalf of the American Kratom Association; *see* http://www.prnewswire.com/news-releases/american-kratom-association-major-new-analysis-shows-no-basis-for-dea-to-restrict-herb-kratom-300371521.html (hereinafter "Henningfield").

[36] "Self-treatment of opioid withdrawal using kratom (Mitragyna speciosa korth)" Addiction. (2008) 103: 1048–1050,

when he added modafinil to promote alertness. In a previous report from 2007[37] Boyer et al. estimated the cost of kratom to be $10-40 per ounce, which means this patient had been consuming on average about 1 to 4 ounces of Kratom per day for 3.5 years – all without negative effects. At 28.35g per ounce, that's an average of between 29.13 to 116.51 grams of Kratom per day, for several years – all without incident. The DEA's 3 factor analysis[38] indicates that 9 grams of Kratom is a high dose (FN 14, pg 13). At the low end of the average estimated dose range, this patient was taking a "high" dose 3 times a day for 3.5 years without any problem.

Among the strikingly few deaths attributed to Kratom, the individual discussed on pages 24-25 of DEA's 3 factor was a 45-year old male who died in 2015 in San Diego, CA, with a level of mitragynine in his liver 200 times that in McIntyre[39] of 0.43 mg/kg. This man's liver had 86 mg/kg (~129 mg of mitragynine for an average 1.5 kg human liver). At 9 mg mitragynine/gram kratom[40], this individual had MG equivalent to *over14 grams of kratom leaf in his liver alone*! He either consumed an enormous amount of Kratom or had an underlying disease that prevented elimination.

The skeptics and agenda-pushing anti-pain pundits may argue that "of course the commentors want Kratom to remain unscheduled – they are using it to get high." I think not. This is exactly the attitude the commentors have experienced daily from a medical establishment so brainwashed against pain treatment that they cannot distinguish fiction from reality. Their cries for help are dismissed as drug-seeking behavior, doctor shopping or worse when making an appointment with a physician for pain, seeking treatment for dependence, filling a prescription at their pharmacy, or even when being treated in an Emergency Department for obvious trauma.

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[37] "Self-treatment of opioid withdrawal with a dietary supplement, Kratom." American J. Addictions / American Academy of Psychiatrists in Alcoholism and Addictions 16:352–356, 2007.

[38] Viewed at https://www.regulations.gov/document?D=DEA-2016-0015-000.

[39] McIntyre et al., "Mitragynine 'Kratom' related fatality: a case report with postmortem concentrations. Journal of Analytical Toxicology 39:152–155, 2014.

[40] *See* Henningfield.

The Downside of Opioids and a Paradigm Shift

At the heart of the debate over pain medication (particularly opioids), treatment of pain (particularly chronic pain), and opioid addiction, is the risk of injury to users.

Among the risks or side effects of opioids reported by the CDC are[41]:

- Addiction
- Physical dependence
- Overdose
- Tolerance
- Increased sensitivity to pain (i.e., OIH)
- Confusion
- Sleepiness and dizziness
- Constipation
- Nausea, vomiting, and dry mouth
- Depression
- Low levels of testosterone (can result in lower sex drive, energy, strength)
- Itching and sweating

If the DEA takes Kratom users at their word, as the agency must if it is to survive a critical evaluation of its validity, Kratom use avoids or minimizes most if not all these side effect. Without such side effects, there is no need to fear, ban or schedule Kratom. The published reports support and are consistent with the user comments if corrected for realistic dosages likely to be consumed by ordinary Kratom users.

Biased Agonism of MG is Consistent with Kratom User Reports

Among the dismal outlook for the state of pain treatment in the U.S., the one thing I have found hopeful and indeed exciting is that the emerging science can ***explain the mechanisms*** by which Kratom alkaloids MG and 7-OH-MG promote analgesia and well-being, without tolerance, addiction, and OIH.

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[41] *See* "Safer, More Effective Pain Management" viewed at http://www.cdc.gov/drugoverdose/prescribing/patients.html.

Key findings which were not considered by the CDC are described in Kruegel et al.[42]. Rather than simply measure the binding affinity of mitragynine to opioid receptors, as previously reported and apparently relied upon by the CDC, Kruegel et al. investigated what MG actually does once it binds. In an elegant series of experiments, the investigators determined that MG acts as a partial agonist (similar to buprenorphine) of the G-protein mediated signal transduction at mu opioid receptors (MOR), but acts as a competitive antagonist of kappa opioid (KOR) receptors and a weak antagonist of delta opioid receptors (DOR).

As summarized in Table 1 of Stein[43] (reproduced below), MOR agonism is responsible for analgesic effect of opioids, and is believed to the primary analgesic mechanism of most commonly prescribed opiods.

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[42] "Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators", J.Am. Chem Soc. 138, 6754–6764, 2016 (hereinafter "Kruegel").

[43] "Opioid Receptors", Ann. Rev. Med., 67:433–51, 2016.

Table 1 Opioid receptors and ligands (adapted from 4 with permission)

Receptor	Site of Action	Effects	Agonist[a]	Antagonist
Mu	Systemic	Analgesia, euphoria, constipation, respiratory depression	DAMGO, morphine, fentanyl, endomorphins, beta-endorphin	CTOP, naloxone
	Peripheral	Analgesia, constipation, reduced inflammation	DiPOA, HS731/AS006, loperamide, frakefamide, DALDA, morphine-6-glucuronide, IQMF-4, SS620	Alvimopan, naloxone methiodide, methylnaltrexone
Delta	Systemic	Analgesia, convulsions, anxiolysis	DPDPE, SNC 80, enkephalins, deltorphin, beta-endorphin	Naltrindole; ICI 174,864; naloxone
	Peripheral	Analgesia, constipation	UK-321,130; ADL5747; ADL5859; JNJ-20788560	Naloxone methiodide
Kappa	Systemic	Analgesia, diuresis, dysphoria	U-69593; U50,488; bremazocine; dynorphin	Norbinaltorphimine, naloxone
	Peripheral	Analgesia, reduced inflammation	Asimadoline, FE200665/CR845, ADL10-0101, CJC-1008, ICI204448	Naloxone methiodide

[a] DAMGO, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin; DALDA, Tyr-Arg-Phe-Lys-NH2; DiPOA, [8-(3,3-diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]-acetic acid; HS-731/AS006, 2-[(4,5alpha-epoxy-3-hydroxy-14beta-methoxy-17-methylmorphinan-6beta-yl)amino]acetic acid; SNC 80, 4-(alpha-(4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide; FE200665/CR845, H-D-Phe-D-Phe-D-Nle-D-Arg-NH-4-picolyl; ADL5747, N,N-diethyl-3-hydroxy-4-(spiro[chromene-2,4′-piperidine]-4-yl)benzamide; ADL5859, N,N-diethyl-4-(5-hydroxyspiro[chromene-2,4′-piperidine]-4-yl) benzamide; JNJ-20788560, [9-(8-azabicyclo[3.2.1]oct-3-ylidene)-9H-xanthene-3-carboxylic acid diethylamide]; ICI204448, (R,S)-N-[2-(N-methyl-3,4-dichlorophenylacetamido)-2-(3-carboxyphenyl)-ethyl]pyrrolidine hydrochloride. All others are proprietary names.

When an agonist such as morphine or DAMGO binds to MOR[44] on the surface of a cell, it triggers conformational change in the receptor that elicits an intracellular signal transduction cascade, which is illustrated in Figure 1 of Stein (reproduced below). G-protein mediated signal transduction at MOR leads to analgesic effects, as well as respiratory depression, euphoria and constipation. Partial agonism as demonstrated by MG[45] may be reflected in less analgesia, but also less respiratory depression, euphoria and constipation.

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[44] MOR, DOR and KOR are cell surface G-protein coupled receptors having 7 transmembrane domains and are often referred to as 7-TM GPCRs.

[45] *See* Kruegel.

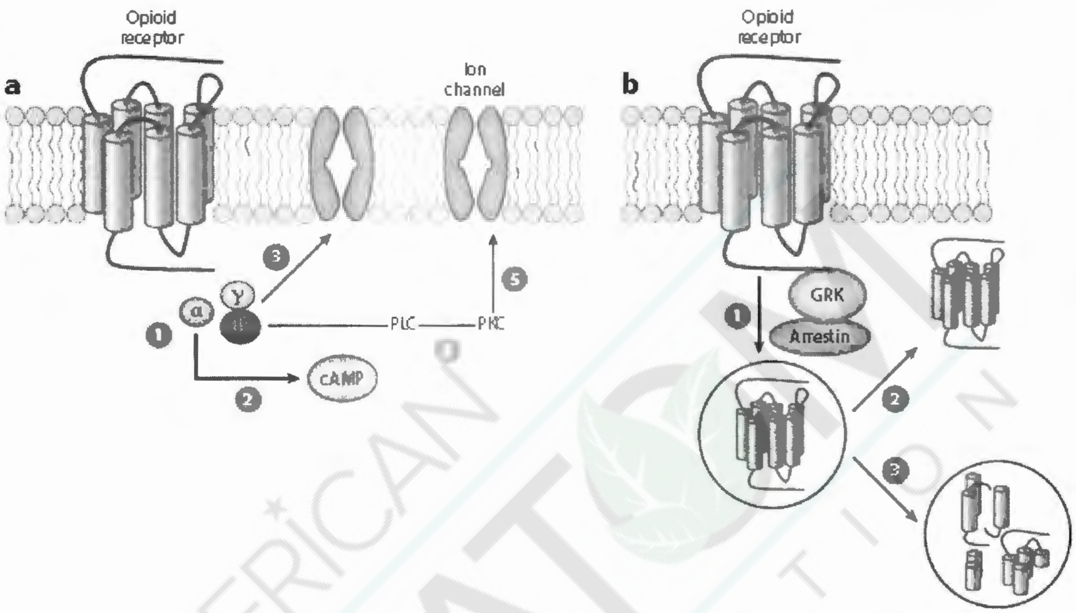

Figure 1

Opioid receptor signaling and recycling (adapted from Reference 9 with permission). (*a*) Opioid receptor ligands induce a conformational change at the receptor that allows coupling of G proteins to the receptor. The heterotrimeric G protein dissociates into active G_α and $G_{\beta\gamma}$ subunits ❶, which can inhibit adenylyl cyclase and reduce cAMP ❷, decrease the conductance of voltage-gated Ca^{2+} channels, or open rectifying K^+ channels ❸. In addition, the phospholipase C/phosphokinase C pathways can be activated ❹ to modulate Ca^{2+} channel activity in the plasma membrane ❺. (*b*) Opioid receptor desensitization and trafficking is activated by G protein–coupled receptor kinase (GRK). After arrestin binding, the receptor is in a desensitized state at the plasma membrane ❶. Arrestin-bound receptors can then be internalized via a clathrin-dependent pathway and either be recycled to the cell surface ❷ or degraded in lysosomes ❸.

Among the additional effects of typical GPCR agonism is recruitment of arrestins, such β-arrestin 2. Recruitment of β-arrestin 2 by MOR leads to desensitization and results in internalization of MOR within the cell. β-arrestin 2 mediated process are believed to be a mechanism for opioid tolerance, which can be understood by considering that when fewer MOR molecules are available on the cell surface for binding to opioid, an increased amount of opioid would be needed to obtain an identical analgesic, G-protein mediated effect. β-arrestin 2 knock-out mice (mice in which the gene β-arrestin 2 has been eliminated) demonstrate the role β-arrestin 2 in analgesia and tolerance: such experimental animal show increased morphine analgesia without the development of tolerance[46]. Thus, elimination of β-arrestin 2 recruitment is a mechanism that has long been sought for reducing tolerance as well as other side effects of opioids.

Kruegel demonstrated that MG effects G-protein mediated signal transduction, but does not recruit β-arrestin 2. Taken together, these results are consistent with a pharmacological profile for MG that exhibits less respiratory depression and low or no tolerance, while providing analgesia – exactly the effects reported by Kratom users.

In peripheral neurons, such biased agonism may explain the reduced or absent opioid induced hyperalgesia similarly reported by Kratom users. In an impressive series of experiments, Rowan et al.[47] investigated the effects of the peripherally acting G-protein biased MOR agonist, herkinorin[48]. The involvement of the Transient Receptor Potential Vanilloid Type 1 (TRPV1, a calcium channel) has been implicated in OIH by a mechanism that also involves β-arrestin 2. In this case, the association of β-arrestin 2 with TRPV1 maintains the channel in a de-sensitized state, while dissociation of β-arrestin 2 sensitizes the channel, thereby producing a pain signal. The investigators found that MOR agonism with DAMGO or morphine recruits β-arrestin 2 away from TRPV1 and induces OIH, but the effects could be reduced by reducing expression of β-arrestin 2 with an anti-sense siRNA. In contrast, herkinorin, a MOR agonist that does not recruit β-arrestin 2, did not sensitize TRPV1 and did not induce OIH in mouse models. These results are consistent with users reports that Kratom is useful for neuropathic pain and do not induce hyperalgesia when used for extended periods of up to many years.

Furthermore, the effects of KOR antagonism are consistent the role as anti-depressants reported by Kratom users. Agonism at KOR induces dysphoria, while KOR antagonists are implicated in treating depression and dysphoric conditions.[49] They may also be

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[46] *See e.g.*, Bohn, et al. "Enhanced Morphine Analgesia in Mice Lacking β-Arrestin 2" Science 286:2495-2498, 1999.

[47] "Activation of Mu Opioid Receptors Sensitizes Transient Receptor Potential Vanilloid Type 1 (TRPV1) via b-Arrestin-2-Mediated Cross-Talk", PLOS-One 9: e93688, 2014.

[48] Herkinorin does not cross the blood-brain barrier and has limited solubility, and therefore has not proven to be a good pharmacological candidate.

[49] Lalanne et al., "The kappa opioid receptor:from addiction to depression,and back" Frontiers in Psychiatry 5:1-17, 2014.

useful in combating addiction. Thus the antagonistic effect of MG on KOR may further explain the effects reported by Kratom users.

Breakthrough Pharmacology

Trevena, Inc. has a developed an analgesic (Oliceridine) that has reduced β-arrestin 2 recruitment, which is currently in phase III clinical trials for i.v. use in post-operative pain[50]. The compound effects analgesia with reduced respiratory depression, and has been awarded "breakthrough status" by the FDA.[51] However, it may be years before this product is available and even longer before an oral formulation that can replace Vicodin or Oxycodone hits the market.

KRATOM IS HERE TODAY.

While we may not understand all the secrets Kratom has yet reveal about pain and analgesia, Kratom has centuries of use demonstrating significantly improved safety over scheduled opioids, and what we do understand increasingly substantiates user experiences. As an herbal supplement, its consumption is self limiting, while offering safe, non-sedating, non-depressant analgesia and a path out of addiction.

There is no reason for DEA to schedule Kratom, and it would be criminal to leave millions of Kratom with no alternatives to pain and suffering, other than a return to increased use of prescription opioids or resorting to illegal purchase on the black market.

Sincerely,

Jane K. Babin, Ph.D., Esq.

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[50] *See* http://www.trevena.com/trevena-pipeline.php.

[51] Crist, "Paradigm Shift: Oliceridine Found Effective for Pain Relief" PainMedicine News, October 16, 2016, viewed at http://www.painmedicinenews.com/Science-Technology/Article/10-16/Paradigm-Shift-Oliceridine-Found-Effective-for-Pain-Relief/38006/ses=ogst?enl=true

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KRATOM'S CURIOUS LEAVES

The science behind kratom's strange leaves

Long used as a painkiller overseas, the plant has gained in popularity among American opioid addicts trying to get clean. Meanwhile, researchers are making headway as U.S. regulators consider cracking down.

By John Arnst

Step into the forest around a rural Malaysian village, pluck the red-, green- or white-veined leaves off a kratom tree, and start chewing. At a small dose, the leaves will act as a stimulant helpful for getting through long hours of hard labor. At a much higher dose, they may cause nausea, vomiting and indigestion, followed by euphoria. At a dose somewhere in between, kratom becomes a highly effective painkiller that can take the edge off after a day's work. It also can stave off the symptoms of heroin withdrawal.

The leaves of Mitragyna speciosa, kratom's Latin name, have been used for centuries throughout Southeast Asia for all of the aforementioned properties. The plants grow wild in Malaysia, Thailand and Indonesia, with related species of the genus Mitragyna ranging as far as India and South Africa.

In the United States, kratom use has surged in the past decade amid the ongoing opioid crisis, which claims dozens of lives each day.

Last fall, the U.S. Drug Enforcement Administration proposed classifying kratom as a schedule I drug. Drugs in that category have no approved medical use, and it is extremely onerous to obtain approval for research on them.

The American Kratom Association, the largest kratom advocacy group in the United States, helped spur an outpouring of public comments. In response, the DEA put a hold on its scheduling plans, and the Food and Drug Administration now is preparing an eight-factor analysis of kratom's safety.

In the meantime, research exploring the interactions of kratom's components with mice and molecular receptors putters on.

Opioid effects

The earliest references to kratom's use as an opium substitute in Western medical literature appeared in 1836, but it has been used for various purposes in Southeast Asia for centuries

WALTERS ART MUSEUM

A mitre made in 1724 by Abraham of Caesarea (present-day Kayseri, Turkey) and presented to the Monastery of the Virgin Mary near Ankara by the city's Armenian bishop Moses. Kratom gets its genus name, Mitragyna, from the leaves' resemblance to these ceremonial hats.

(see box "Plucked from the branch").

Mitragyna speciosa belongs to the same family, Rubiaceae, as coffee plants and gets its genus name from the leaves' resemblance to a bishop's ceremonial hat, called a miter.

The leaves from kratom trees contain at least 37 different alkaloids, a class of nitrogen-atom-containing compounds, but they have two primary active components: mitragynine and 7-hydroxymitragynine, or 7-OHMG, an oxidized analog of mitragynine.

The term "opiate" traditionally has been used to describe drugs derived from opium extracts of poppy plants; "opioid" refers to compounds, such as hydrocodone, that bind to the same receptors in the human brain and body that opiates do. The mitragynine compounds work, in part, by binding to these receptors, which come in three major subtypes.

"The first one is mu — we use the Greek letter mu to signify morphine. Morphine was particularly good at this receptor subtype, and to this day the mu receptor is a predominant one," says Solomon Snyder. A neuroscientist at Johns Hopkins University, Snyder and colleague Candace Pert characterized the mu opioid receptor for the first time in 1973, for which Snyder won the Lasker Award in 1978.

The kappa receptor was named for its affinity for the drug ketocyclazocine; the delta receptor was initially discovered in the vas deferens tissue of mice. Due to a high sequence similarity with the original three opiate receptors, the receptor for the neuropeptide nociceptin often is referred to as a fourth, but it actually exhibits minimal binding activity with opioids.

"The hope was that perhaps these sites were responsible for analgesia, euphoria and, separately, for addiction, and that we could separate them out and get nonaddictive opiates," says Snyder. "There's been a lot of progress in having less-addicting opiates based on understanding receptor pharmacology, but to this date, there aren't any truly nonaddicting opiates on the market."

Heroin and morphine kill by causing respiratory depression, in which the muscles that control the diaphragm fail and breathing ceases. These overdoses can be reversed if the drug naloxone is administered within a few minutes, before irreversible brain damage sets in. Sold as Narcan, naloxone acts as an opioid receptor antagonist by essentially kicking the other opioid compounds off the opioid receptors.

According to Andrew Kruegel, a medicinal chemist and opioid researcher at Columbia University, one hypothesis in the opioid field is that fatal respiratory depression, or failure, occurs as a consequence of compounds working through the mu receptors to activate the protein

CONTINUED ON PAGE 22

DARSHAN SINGH/UNIVERSITY OF SCIENCE MALAYSIA

The leaves of kratom plants in Malaysia contain at least 37 different alkaloids.

Plucked from the branch

While human studies involving kratom haven't taken place in the U.S., the plant's prevalence on the other side of the Pacific Ocean allows for a wealth of observational studies in Malaysia, where the plant is nominally illegal under an amendment to the Poisons Act of 1952.

According to Darshan Singh, an epidemiologist at the University of Science Malaysia, kratom users in Malaysia generally fall into three groups.

Older, rural kratom users typically use the plant for its low- and medium-dose effects as a stimulant and painkiller, respectively. "If you look at the rural areas, you get to see people cultivating their own kratom tree behind their house. Cultivation of kratom trees is not a serious offense in Malaysia, but possession and misuse of kratom leaves can put someone in serious trouble with the law. So if they want to use kratom or they want to drink kratom juice, they will just have to pluck fresh kratom leaves and boil it for personal consumption," says Singh.

Younger users seeking a high consume kratom in a beverage called chakroi that combines processed kratom juice with cough syrup, which contains the antihistamine diphenhydramine. Because juice from kratom leaves tends to be bitter, Singh says, the users typically add Coke or Pepsi as a caffeine-containing sweetener. The beverage is also popular in Thailand, where it's known as 4X100, or sii koon roi. Thailand has reported one death involving kratom consumption.

"Nobody has died because of kratom use in Malaysia," says Singh. "You also have illegal kratom traders in the community, people who are selling fresh kratom juice, but it's actually very safe."

The third group of kratom users bears the most resemblance to those in the United States. "They use kratom to self-treat their heroin-addiction problem," says Singh. "I get to see a lot of heroin users who are on methadone treatment. They don't want to use methadone, because methadone has a lot of side effects." Instead, they turn to kratom.

Singh has been monitoring the health impacts of long-term kratom use, which he defines as 10 years of moderate consumption or five years of heavy consumption — around four glasses of boiled kratom juice each day. He and his colleagues at the Center for Drug Research recently completed clinical evaluations of a substantial number of regular kratom users and are preparing to publish the results. They will be soon conducting a study to document the prevalence of kratom use in illicit drug users in Malaysia.

"We found that long-term kratom use does not cause major psychiatric problems like methamphetamine or heroin," says Singh. "The only problems that you see are slight anxiety and depression problems during kratom cessation in regular kratom users."

He and his colleagues also noted that long-term kratom use doesn't appear to cause any cognitive impairment. "There is no impairment in memory, there is no impairment in attention — nothing," he says.

Despite these findings, Singh is concerned that Malaysian authorities might reclassify kratom from its current status as a poison to that of a fully outlawed compound. "They're in limbo over whether to do that or not, because they see a lot of people are misusing kratom, but I'm trying to make them understand that people who are misusing kratom are people who were dependent on illicit drugs before, and they are beginning to use kratom to treat their dependence," he says.

In the Malaysian countryside, shown here in an aerial view, some residents cultivate their own kratom trees.

CONTINUED FROM PAGE 20

beta-arrestin. When this happens at a certain threshold, a cascade of signaling that interferes with the action of the diaphragm is believed to occur.

Both mitragynine and 7-hydroxymitragynine are partial agonists for the mu receptors, binding to and activating them at less than 100 percent of the levels that other opioids, such as morphine, do. As Kruegel and colleagues observed in in vitro systems, beta-arrestin signaling is notably absent in this activity and thus may be responsible for kratom's anecdotally reported ability to induce less respiratory depression than heroin or morphine.

The mitragynines are also both antagonists of the kappa and delta opioid receptors in in vitro systems, meaning they reverse the effects of pain-killing analgesics at these sites, but these actions aren't yet understood in human or animal models. These receptor interactions also are hypothesized to be responsible for kratom users experiencing reduced euphoric effects and slower development of tolerance compared to those experienced with widely abused opioids.

Similar partially agonistic effects of the mu receptors are also present in buprenorphine, an opioid marketed as Buprenex and Butrans and widely used in clinics and addiction centers to help patients transition off fully agonistic opioids like heroin and morphine.

Although buprenorphine can cause a degree of respiratory depression, the compound is used in clinics because it takes an extremely high dose to induce respiratory failure. “Clinical studies have shown that (buprenorphine) has a ceiling on respiratory depression,” says Kruegel, who is examining the interactions between the components in kratom and the human opioid receptors. “You can almost think of mitragynine as buprenorphine light.”

Why kratom doesn't appear to be as addictive as opioids, however, is not clear. Even if shutting down beta-arrestin signaling does stop respiratory depression, it doesn't appear to be responsible for how addictive an opiatelike substance is.

“If you get rid of beta-arrestin signaling, it's not like you're going to have a nonaddictive opioid,” says Kruegel. “There's a very big obsession, I would say, in the field of getting rid of the addictive properties, but I think what we should focus on is just not killing people to start with. If you get rid of respiratory depression, you're saving 18,000 lives a year from opioid overdose, so that's a huge improvement.”

Forgotten pharmacology

Mitragynine first was isolated from kratom leaves in 1921 by Ellen Field, a medicinal chemist at the University of Edinburgh, and its structure was first characterized by X-ray crystallography in 1964 by a group led by G.A. Jeffrey at the University of Pittsburgh.

Across the Atlantic, Joseph Shellard and Arnold Beckett at Chelsea College, London, had been examining the chemical structures of known and novel alkaloids in Mitragyna speciosa and other Mitragyna species since 1961 with Ph.D. students David Phillipson and Albert Tackie.

“The major interest was in Mitragyna speciosa, known as kratom, because it was used as a substitute for opium or as a cure for opium addiction in (what was then called) Malaya and Thailand,” says Peter Houghton, a retired pharmacognosist who also performed his Ph.D. work with Shellard.

According to pharmacognosist Phillipson, now retired, there was interest in the 1960s from the pharmacy company Smith Kline French, later merged into GlaxoSmithKline,

AMERICAN KRATOM ASSOCIATION

Kratom flowers grow in clusters at the end of the trees' branches.

Branches bursting with secrets

While mitragynine, 7-hydroxymitragynine and a few dozen other alkaloids make up the bulk of the 57 phytochemicals that have been isolated from kratom leaves, the plants contain a panoply of currently unidentified compounds and metabolites.

“The average plant leaf is somewhere between 35,000 and 50,000 distinct phytochemicals, and we really can identify about 1,000 if we’re lucky,” says Susan Murch, a chemist at the University of British Columbia. “You’re looking at a minimum 34,000 unknowns. In your glass of merlot, you’re looking at 7,000 unknowns; in your cup of coffee, over about 6,800 unknowns.”

Identifying these unknown compounds and mapping their enzymatic relationships to one another by use of mathematical equations is known as metabolomics; each study can take up to three to four years due to its scale. “You do a very small mass spec analysis, and then you spend a year mining data. It’s a massive bioinformatics program,” says Murch.

Murch recently published a literature review in the Journal of Ethnopharmacology that detailed the history and chemistry of kratom and its sister species in Western medical literature with Web of Science, Google Scholar, the Royal Museum for Central Africa, the Internet Archive, the Hathi Trust and the Biodiversity Heritage Library.

Murch and her collaborator Paula N. Brown are hoping to get a metabolomics study involving kratom up and going within the next few years. “There are no metabolomics studies out there that really are definitive in terms of the different varieties, the different strains, the different things people are using,” she says.

Identifying the thousands of unknown metabolites, or intermediary components, within kratom leaves will be essential to understanding how the plant products are differently processed by populations across the globe.

“Kratom is traditionally used by a fairly specific population of Vietnam, Thailand and Southeast Asia, and so we don’t know about its nutrigenomics effects,” says Murch. “Assuming that a population in Southeast Asia will respond the same as a population anywhere else in the world is a bit of a leap of faith.”

WIKIMEDIA COMMONS USER THORPORRE

The leaf of Mitragyna speciosa contains at least 34,000 unknown phytochemicals.

to develop mitragynine as a painkiller to replace morphine. After its potency as an analgesic was found to be more comparable to that of codeine, he says, “they thought, ‘Codeine is big business, and if this is an analgesic, then maybe it will replace codeine.’ But they did toxicity tests, and they found that mitragynine was toxic to beagle dogs, and that killed the project stone dead.”

At the time, Phillipson says, the researchers at Chelsea didn’t have enough mitragynine to undertake pharmacological research. “We obviously wanted to become involved in biological activity, and that meant collaborating with pharmacologists who would say, ‘Send me 10 grams of what you’ve got,’ but we only had 10 milligrams, and all of those have large numbers of alkaloids,” says Phillipson.

In his time with Shellard, Phillipson isolated 16 alkaloids from M. speciosa and four other Mitragyna species (for more information about kratom’s chemical components, see box “Branches bursting with secrets”).“Eight of these (alkaloids) were not previously isolated from

Mitragyna, and five of them were, in fact, novel alkaloids, and I was interested in the determination of their chemical structure," he says.

In his subsequent research, Phillipson investigated the alkaloids of Uncaria species, which are closely related to Mitragyna, as well as alkaloids of Cinchona species, the source of the antimalarial medicine quinine. All three genera belong to the same botanical family, Rubiaceae.

With interest from pharmaceutical companies gone, research into Mitragyna alkaloids as novel analgesics was halted for a number of decades.

Strange brews

Given that kratom is currently legal in the U.S., the biggest medical concern is the potential adulteration of products being sold as kratom. "The issue becomes: What degree of confidence does someone have, when someone says they're taking kratom, that they're actually taking kratom?" says Edward Boyer, a professor of emergency medicine at Brigham and Women's Hospital and faculty member at Harvard Medical School.

"In the United States, there's nothing to protect people from an adulterated product. Even truthfully, if they bought it in a store, the Dietary Supplement Health and Education Act of 1994 essentially prohibits any regulatory agency from doing anything to prevent a tainted product from reaching the marketplace," Boyer says. "The FDA has to prove that something is unsafe, and that's something, candidly, that the FDA never does."

In a study published in the Journal of Medical Toxicology in 2016, Boyer and his colleagues found that a number of kratom products from a major kratom distributer based in Miami had concentrations of 7-hydroxymitragynine that were elevated notably compared with kratom leaves.

While there haven't been any recorded deaths from overdoses resulting solely from kratom in the United States, there have been at least three deaths caused by overdosing on mixtures of kratom and other controlled substances. In addition to one death in Norway and another in Thailand, there have been nine deaths in Sweden caused by the drink "krypton," which consists of kratom mixed with an active metabolite of the controlled painkiller tramadol.

A report from the Centers for Disease Control and Prevention published last year noted a significant increase in kratom-related calls to poison control centers between 2011 and 2015, with 49 of 660 recorded calls about kratom classified as major or life-threatening.

Additionally, legislation to outlaw the plant and its compounds was passed in Sarasota County, Florida, in 2015 after the suicide of a teenager whose toxicology report turned up positive for kratom and antidepressants. Subsequent bills were introduced in 2016 and 2017 but were strongly opposed by activists, including the American Kratom Association, and failed to pass the state legislature.

American limbo

If kratom were placed in schedule I, "the most dangerous marketers in the world would take over. They would fill the niche with black market, and they would be likely to mix it with other things," says Jack Henningfield. Henningfield is an associate professor at the Johns Hopkins University and a vice president at the health consulting firm Pinney Associates.

When the DEA announced its intent last fall to place kratom in schedule I, which includes marijuana, LSD, psilocybin, heroin and bath salts, among other compounds, the American Kratom Association

EMILY HUFF/ASBMB

Kratom leaves are sometimes ground and sold as a powder.

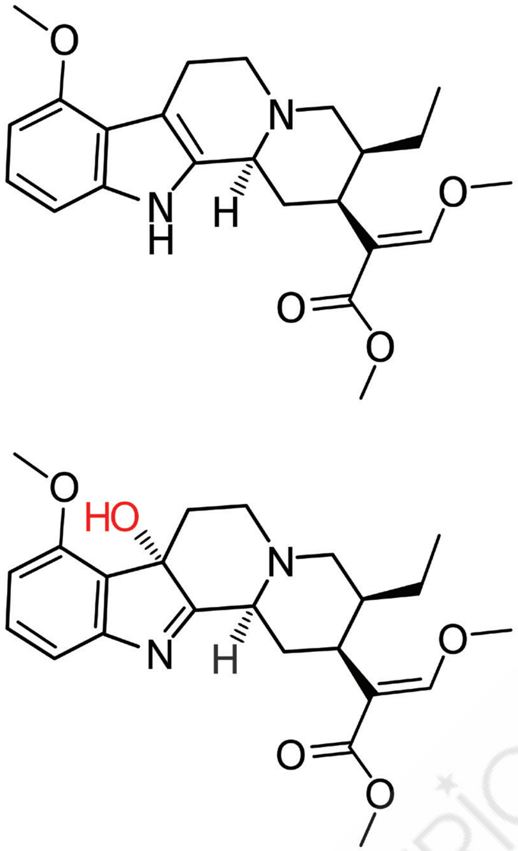
contacted Henningfield by way of the D.C.-based law firm Hogan Lovells.

"We said, 'Look, the train has left the station. The DEA will never change its opinion on this. They have yet to withdraw a scheduling proposal, as far as I know, in history,'" says Henningfield. "Nonetheless, we will help you as we can to oppose this action, because it carries serious public health risks."

Henningfield and his colleagues previously had performed a safety analysis on kratom for another client that had been seeking to market a dietary supplement using the plant and have experience with the Controlled Substance Act's eight-factor analysis used by the DEA and FDA to guide the regulation of potentially abusable and addictive substances, including medicines. The analyses examine eight factors of a substance relevant to scheduling: pharmacology; potential for abuse; history and current pattern of abuse; public health risk; dependence liability; scope, duration and significance of abuse; status as an immediate precursor of a controlled substance; and other current scientific knowledge.

"Like a lot of things, you could schedule it. If caffeine was a brand new drug discovered today and you brought it to the FDA, it would probably be proposed for a schedule III or IV," says Henningfield. "It produces dependence, it's a reinforcer, it produces pleasure, it produces physical dependence and there are withdrawal symptoms, and more."

Instead of scheduling kratom, an ideal regulatory model would be the one used for caffeine, Henningfield



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Skeletal formulas of mitragynine (top) and 7-hydroxymitragynine (bottom), with the latter's hydroxyl group in red.

says, in which a certain number of milligrams of caffeine are permitted by volume for beverages, but beans can be purchased directly to make coffee.

"Saying that it shouldn't be scheduled isn't saying that nothing should be done," says Henningfield. "I think that we need information for people, labeling, oversight of the marketplace and standards that get the potential problem off the market."

While FDA officials declined to comment for this story, the press office did say that the analysis "will be provided to DEA through (Health and Human Services) as expediently as possible."

Box of leaves

While the FDA deliberates, the pending scheduling has upended the projects of scientists who were working with kratom.

Christopher McCurdy, who was at the University of Mississippi's National Center for Natural Products Research when the scheduling was proposed, was using mouse models to investigate kratom's efficacy as a potential treatment for opioid withdrawal syndrome. A medicinal chemist, McCurdy has collaborated with Boyer on a number of papers, including the adulteration study.

In one experiment, McCurdy and his colleagues gave mice two doses of morphine daily for five days, doubling it each day until the mice were habituated to the substance, in order to assess kratom's ability to prevent the symptoms of opioid withdrawal. In a normal model, the mice would then receive an opioid antagonist, such as naloxone, which is the substance used to reverse heroin overdosing, and then go through physical symptoms of opiate withdrawal. When the researchers put the mice through a five-day regimen of freeze-dried kratom tea before precipitating withdrawal, however, the animals displayed a significant reduction in side effects that was greater than that observed with methadone.

The model was subsequently repeated with extracts of pure mitragynine in place of kratom tea, which caused the residual side effects of withdrawal to vanish completely. "In the mitragynine-treated animals, we saw absolutely no withdrawal symptoms after five days," says McCurdy.

When the ban came down, McCurdy and the pharmacologist Bonnie Avery, a collaborator who performed the analytical work on the adulteration study and prepared the dosing information for the mice models, were working on developing kratom as a botanical drug. Botanical drugs are a class created by the FDA for drugs consisting of vegetable materials with complex mixtures that can be consumed as powders, tablets, solutions and the like.

"We had to stop everything we were doing because of the pending scheduling," says McCurdy. "We literally packed up 12 years' worth of research and shipped it to one of our collaborators that does have a schedule I license, just in case the DEA decided to announce that it was schedule I. We would have had enough material in our possession to be considered as one with intent to distribute, so I didn't want to be on the illegal list all of a sudden."

McCurdy's kratom supplies are currently in the hands of his colleague Scott Hemby, a pharmacologist at High Point University in Highpoint, North Carolina. McCurdy and Avery, who are married, recently relocated to the University of Florida in Gainesville, and are both currently faculty members in its College of Pharmacy.

"He sent me raw material — literally a box full of things," says Hemby, who has had a schedule I license and worked with controlled substances such as heroin and cocaine for several years. Since receiving the kratom from

McCurdy, Hemby has performed a number of experiments with mitragynine and 7-hydroxymitragynine in rats.

In one self-administration experiment, Hemby and his colleagues trained rats to press a lever to receive intravenous infusions of morphine. Due to the opiate's euphoria-inducing effects, the rats would continue pressing the lever to receive morphine. After three doses, the researchers replaced the morphine with saline, at which point the mice stopped pressing the lever. When the researchers then replaced the saline with mitragynine or 7-hydroxymitragynine, they noticed something strange.

"The animals really wouldn't respond if you gave them mitragynine," says Hemby. "But if we looked at 7-hydroxymitragynine, they would self-administer. So it was interesting that one of these compounds does seem to have some abuse liability and the other one doesn't, at least in this substitution paradigm."

A more disconcerting disparity between the two mitragynine compounds appeared when Hemby and his colleagues once again exposed rats that had gone through the same procedure to morphine.

"We gave them access to morphine again, and, interestingly, they increased their morphine intake two- to three-fold after they had a history of 7-hydroxymitragynine," says Hemby. "Some of the newer imports are being spiked with 7-hydroxy, and that may increase subsequent morphine intake. That's one of the subsequent concerns that we have … there are a lot of things we just simply don't know about the mechanism behind what's going on here."

A scaffold for the future

Five floors down from McCurdy's office in the College of Pharmacy, his collaborator Jay McLaughlin is working with Susruta Majumdar at the Memorial Sloan-Kettering Cancer Center in New York to develop novel analgesics based on kratom's molecular scaffolding.

Majumdar and McLaughlin recently published a paper in the Journal of Medicinal Chemistry detailing the analgesic effects of the modified kratom analog mitragynine pseudoindoxyl.

When Majumdar and his colleagues examined the analog's efficacy in mouse models, "we found that it's a potent analgesic, three to five times more potent than morphine," says Majumdar.

The researchers also examined its efficacy as a delta receptor-antagonist, which is a property that causes users to develop less of a tolerance to a drug that acts as a mu agonist. Across the board, pseudoindoxyl appeared to be a more potent delta antagonist in isolated in vitro receptors than either mitragynine or 7-hydroxymitragynine.

"Mitragynine pseudoindoxyl is also the first molecule in a kratom-derived template that shows no abuse potential and has far reduced respiratory depression (compared to) all clinically used opioids in mice, possibly because of its non-beta arrestin recruiting mechanisms," he says.

Despite these benefits, "mitragynine pseudoindoxyl is more of a therapeutic for tomorrow," he says.

In the meantime, McLaughlin is hoping to begin studies at the University of Florida with Avery and McCurdy examining pharmacodynamic properties of mitragynine pseudoindoxyl, such as its longevity in the body, byproducts and mechanisms of elimination.

Foliage frontiers

The earliest noted record of kratom use in the United States appeared in the 1999/2000 issue of the now-defunct quarterly publication Entheo-

CHRISTOPHER MCCURDY/UNIVERSITY OF FLORIDA

Kratom trees are grown at the University of Mississippi's National Center for Natural Product Research. The trees can reach up to 15 meters.

gen Review, a self-described "Journal of Unauthorized Research on Visionary Plants and Drugs" that ran in a confidential, underground manner from 1992 to 2008.

Today, researchers are starting to get a better idea of the demographic groups using kratom in the U.S. and their reasons for doing so. Oliver Grundmann, a toxicologist and pharmacologist at the University of Florida, recently published the initial findings from a survey of 10,000 self-reported kratom users conducted with the assistance of the American Kratom Association. The paper appeared in the journal Drug and Alcohol Dependence.

Grundmann and his colleagues found that, out of the 8,049 kratom users who completed the entire survey, less than 1 percent had experienced physical or psychological incidents that required hospitalization or treatment by a physician.

"That was a very low incidence rate, overall, compared to many other drugs … even among those that are common prescription drugs," says Grundmann. The authors also found that, while 68 percent of kratom users were using it to self-treat pain, some 66.5 percent were using it to self-treat conditions such as anxiety, depression or post-traumatic stress disorder.

"I've found that these effects, especially, were not necessarily as dose-dependent as some of the other effects, like the analgesic effects," says Grundmann. "So I think that people that are taking it for the mood-elevating effects, the antidepressant effects, are not necessarily at as high of a risk of getting used to or dependent to kratom as those that are taking it for the analgesic effects or for treating opiate withdrawal symptoms."

Kruegel and his colleagues at Columbia are seeking to demystify some of these interactions by exploring the receptor activities of kratom's other major compounds, speciociliatine, speciogynine and panatheine, as well as elucidate mitragynine and 7-hydroxymitragynine's interactions with the receptors to which serotonin and adrenaline molecules bind.

For the field, Grundmann says, the next stage should be human clinical trials with well-defined chemical extracts of kratom's mitragynines and other alkaloids.

"If (clinicians) go down the route and want to use pure mitragynine and 7-hydroxymitragynine, then what we're looking at is basically a synthetic drug derivative, like mitragynine or 7-hydroxymitragynine. Is that what we want? That's the question: Do we want kratom to basically become a scaffold, a framework for a synthetic drug down the road, or do we want kratom extracts to remain more of a supplement that is an extract, but with a special quality standard that is established?"

At the moment, there are no concrete plans or proposals for researchers wishing to carry out clinical trials of kratom or mitragynine compounds. Grundmann is continuing to mine the survey data and hopes to have another paper published within the year.

In the meantime, medical opinion on kratom use may be shifting as regulatory agencies idle.

Among the 8,049 self-reported kratom users in Grundmann's study, 40 percent had discussed their kratom use with their health care providers.

"I think that even within the medical community it has kind of reached a point where it's 'give it a try, kind of, and see if it is successful,' instead of flat-out denying its existence or just saying it's no good," says Grundmann.

"The larger discussion is: How do we, as a society, respond to drugs in general, right?"

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Capsules of kratom can be purchased in varying quantities online, at herb shops and even from vending machines in certain U.S.locations.

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Update on the Pharmacology and Legal Status of Kratom

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Kratom (*Mitragyna speciosa*) is a plant indigenous to Southeast Asia. Its leaves and the teas brewed from them have long been used by people in that region to stave off fatigue and to manage pain and opioid withdrawal. In a comprehensive review published in 2012, Prozialeck et al presented evidence that kratom had been increasingly used for the self-management of opioid withdrawal and pain in the United States. At the time, kratom was classified as a legal herbal product by the US Drug Enforcement Administration. Recent studies have confirmed that kratom and its chemical constituents do have useful pharmacologic actions. However, there have also been increasing numbers of reports of adverse effects resulting from use of kratom products. In August 2016, the US Drug Enforcement Administration announced plans to classify kratom and its mitragynine constituents as Schedule 1 controlled substances, a move that triggered a massive response from kratom advocates. The purpose of this report is to highlight the current scientific and legal controversies regarding kratom.

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In December 2012, I was the lead author of a review published in *The Journal of the American Osteopathic Association* that focused on an emerging botanical agent called kratom.[1] The species, *Mitragyna speciosa*, is a tree indigenous to Thailand and other areas of Southeast Asia.[2] When ingested or consumed in the form of teas, kratom leaves produce complex dose-dependent stimulant and analgesic effects.[1] In Southeast Asia, kratom has been used to stave off fatigue and to manage pain, diarrhea, cough, and opioid withdrawal.[2-6] Our analyses of the medical literature and websites in 2012 revealed that kratom had been increasingly used for the self-management of opioid withdrawal and pain in the United States. We also reported on the pharmacologically active constituents of kratom, most notably mitragynine, 7-hydroxymitragynine, paynantheine, and speciogynine, along with more than 20 other substances.[1,3] These compounds have complex and potentially useful pharmacologic activities. In addition, we found many anecdotal reports and testimonials posted online suggesting that kratom may have beneficial effects, particularly in the management of both opioid withdrawal and pain.[1]

At the time our review was published, kratom was not banned by the US Drug Enforcement Administration (DEA), although it was on their Drugs and Chemicals of Concern watch list.[1,7] We summarized the potential therapeutic benefits of kratom, but we also emphasized that no well-controlled scientific studies on the safety and efficacy of kratom had

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been published.[1] We noted an increase in the number of reported adverse effects attributed to kratom and highlighted the lack of regulation and quality-control measures in the production and sale of kratom products. Our conclusions from these analyses were that even though kratom or its active constituents could have potential for development as therapeutic agents, it would not be appropriate for physicians to recommend kratom for their patients.

In the 4 years since the review[1] was published, several major developments have been made regarding the pharmacology and legal status of kratom.[8] Given the widespread use of kratom and the extensive media attention it is receiving,[8-11] it is important for physicians and other health care professionals to be knowledgeable about the subject. The purpose of this review is to update readers about key developments in this rapidly evolving area.

Legal Status of Kratom

The most controversial development regarding kratom is the recent decision by the DEA to classify kratom and the kratom-derived drugs, mitragynine and 7-hydroxymitragine, as Schedule 1 controlled substances.[8] Over the years, kratom has been regulated as an herbal product under US Food and Drug Administration and DEA policies. As such, it has been considered a legal substance in most of the United States, although a handful of states, such as Alabama, Florida, Indiana, Arkansas, Wisconsin, and Tennessee, have recently passed legislation banning the local sale and possession of kratom.[9,10]

Despite the uncertainties regarding the legal status of kratom, over the past 4 years it is apparent that kratom use in the United States has increased measurably. More than half of all literature on kratom has been published in just the past 4 years. In our 2012 review,[1] we reported that a search of the US National Library of Medicine's PubMed database, using the keyword *kratom*, yielded a total of 35 published articles and reviews. A similar search conducted in October 2016 showed that 44 additional articles had been published. Results of several analyses[4,11,12] published within the past year indicate that large numbers of people are using kratom for the management of opioid withdrawal and pain. A cursory review of the many patient comments on websites such as The Vaults of Erowid,[13] Sage Wisdom,[14] and Speciosa[15] indicates that many users believe that kratom has been a relatively safe and effective way to manage these conditions. However, no controlled clinical trials on the safety and efficacy of kratom have been published. At the same time, increasing numbers of adverse effects and toxic reactions associated with the use of kratom products have been reported.[8,16,17]

It was in the context of these uncertainties regarding safety and efficacy of kratom that, in August 2016, the DEA announced its plans to move kratom and mitragynines to Schedule 1 status.[8] This category includes drugs such as heroin and LSD, which have no valid medical uses and a high potential for abuse. The DEA's announcement sparked vigorous opposition from many patients and patient advocacy groups who claim that kratom had helped them manage opioid withdrawal or chronic pain.[9-11,18,19] The advocates' responses included a march and demonstration at the White House on September 13, 2016, and a petition with over 130,000 signatures that was sent to President Barack Obama. In addition, several congressional representatives and US senators signed letters asking the DEA to reconsider the kratom ban, which was to go into effect on September 30, 2016.[20,21] In response to these challenges, the director of the DEA announced that the kratom ban would be temporarily placed on hold.[21-23] All of these events have received extensive coverage by news media and have raised public awareness of the issue. As a result of my familiarity with kratom, I have been contacted by several news reporters and writers for my thoughts and opinions about the kratom controversy.[9-11,18,19] Even though there are far more questions than answers, I hope that I can accurately frame some of the most important questions.

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The 2 most obvious questions are “why is kratom so controversial?” and “why is the DEA planning to ban it?” From my analysis of the literature[1] and the DEA’s announcement,[8] it is readily apparent that the controversies and the DEA’s position are based on the reported opioidlike effects of kratom, questions about its toxicities and addictive potential, and uncertainties about its efficacy and safety in the management of opioid withdrawal and pain.

Should Kratom or Its Mitragynine Constituents Be Classified as Opioids?

In describing their rationale for banning kratom, the DEA emphasized that kratom and mitragynines have been reported to produce some opioidlike effects. Most of the scientific evidence that kratom may have opioidlike activity is derived from the results of animal studies and ligand-binding studies, which have suggested that mitragynines may interact with opioid receptors.[1,3,24,25] In addition, anecdotal reports and commentaries indicate that some of the effects of kratom in humans resemble those of opioid agonist drugs.[4,5,26] Although no well-controlled clinical trials have been done, strong evidence demonstrates that the effects of kratom are actually quite different from those of classic opioids.[4,5,26] For example, at low to moderate doses, kratom has mild stimulant properties, unlike opioids, which are mainly sedating. In addition, kratom does not usually produce an intense high or euphoria.[1,2,13-15] Importantly, even at very high doses, kratom does not depress respiration.[4] At the molecular level, mitragynines are structurally quite different from traditional opioids such as morphine.[1,27] Moreover, recent studies indicate that even though the mitragynines can interact with opioid receptors, their molecular actions are different from those of opioids. In 2 elegant studies, Váradi et al[28] and Kruegel et al[29] showed that several mitragynine analogs acted as agonists at μ opioid receptors and antagonists at δ opioid receptors. Most notably, even though they activated the G-protein–mediated signaling pathway, much like traditional opioids, they did not “recruit” β-arrestin-2, which has been implicated as a mediator of opioid side effects and dependence.[30] Using a mouse model, Váradi et al[28] showed that kratom-based drugs had marked analgesic effects but with far fewer side effects, slower development of tolerance, and lower potential for dependence than morphine. Based on all of the evidence, it is clear that kratom and its mitragynine constituents are not opioids and that they should not be classified as such.

Is Kratom Effective for the Management of Opioid Withdrawal or Pain?

The current epidemic of opioid abuse and addiction in the United States has recently been highlighted in several major commentaries,[31-33] and it has prompted action by the federal government and the Centers for Disease Control and Prevention. The most decisive action has been the development of new guidelines by the Centers for Disease Control and Prevention for the prescribing of opioids.[34] In this environment, physicians are being discouraged from prescribing opioids, especially for long-term use, and patients with chronic pain conditions are seeking alternatives.[11,12] In addition, many patients who have taken opioids for chronic pain are seeking alternatives that lack the side effects and addiction potential of opioids.[11,12] Many people have turned to kratom with the belief that it may provide an effective and reportedly safe alternative to prescription or street opioids. It should be emphasized that most of these claims are on websites such as The Vaults of Erowid,[13] Sage Wisdom,[14] and Speciosa.[15] The few scientific studies that have addressed this issue have been summaries of patient experiences or clinical reports.[4,6,12] Swogger et al[12] conducted a systematic analysis of kratom user reports on The Vaults of Erowid website.[13] Whereas some users reported negative effects, particularly nausea and vomiting, mainly from higher doses, the vast majority of users reported beneficial effects in the management of opioid withdrawal and pain, depres-

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sion and anxiety. I find the many positive experiences on The Vaults of Erowid, Sage Wisdom, and Speciosa websites to be compelling. In my opinion, the therapeutic potential of kratom is too large to be ignored. Well-controlled clinical trials on kratom or the many active compounds in kratom are needed to address this issue.

One strong piece of evidence suggesting that kratom may have extensive therapeutic potential is that several US patents have either been issued or are pending for companies and individuals who are interested in developing kratom-based drugs.[35-37] These patents would not have been submitted or issued unless there was evidence for medicinal applications of kratom-derived substances.

Before considering the potential use of kratom in the management of opioid withdrawal, several major therapeutic controversies need to be addressed. Many kratom advocates have claimed that kratom is a safe and effective alternative to opioids for the management of opioid withdrawal.[4,13] However, some addiction treatment specialists have noted that kratom may be a "crutch" or a "gateway" drug that can increase the likelihood that individuals will graduate to hard-core opioids such as heroin.[10] In this regard, it is not clear how kratom would be any different from agents such as methadone and buprenorphine, which are widely used as maintenance agents in the management of opioid withdrawal even with their great potential for abuse.[38] This issue is at the center of a major debate in addiction medicine. Should the goal of treatment be abstinence or harm reduction?[39] If the goal is harm reduction, kratom may have a potential role, especially because kratom is less toxic than drugs such as methadone.

How Serious Are the Abuse and Addiction Potentials of Kratom?

Studies have shown that people may seek kratom for its mind-altering effects and, with long-term use, may become dependent or addicted.[25,40,41] Even though these reports indicate that the effects as well as withdrawal symptoms from kratom can resemble those of opioids, many users have reported that the subjective effects of kratom are different from those of opioids. As noted previously, low to moderate doses of kratom tend to be somewhat stimulating and do not produce the "high" or euphoric effects associated with opioids.[4,12-15] In addition, many users have reported that withdrawal symptoms from kratom are much milder than symptoms from traditional opioids.[4,13,41] Most notably, even at high doses, kratom does not depress respiration as do traditional opioids.[4,41] Although kratom has potential for abuse and addiction, several investigators who closely examined these issues concluded that kratom is not as dangerous as traditional opioids and that the potential benefits may outweigh the risks.[4,12,26,41]

Are Kratom Products Safe?

With the increasing use of kratom in recent years, the number of reports of adverse effects resulting from the use of purported adulterated "kratom" products has also been increasing.[16,17,42,43] These reports were cited as one of the major concerns in the DEA's decision to ban kratom.[8] At low to moderate doses (5-10 g of raw leaves), the adverse effects vary markedly from one person to another, but they generally appear to be mild.[1,4,16,41] The most common effects are anxiety, irritability, nausea, and vomiting.[1,12,16,41] More troubling have been reports of serious toxic reactions associated with high doses or the use of concentrated extracts. Some of the reported effects include tachycardia, seizures, and liver damage.[44-48] In addition, there have been several deaths attributed to the use of purported kratom products.[8,16,43,49-51]

From the foregoing summary, it is understandable why the DEA would be concerned about the safety of kratom. However, several factors need to be considered in evaluating whether the DEA's proposed ban is justified. First are the simple statistics. When it announced the decision to ban kratom, the DEA emphasized that between January 2010 and December 2015, 660 calls had been made to poison control centers regarding

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adverse reactions to kratom products.[8] This might seem to be an alarming number, but it is rather small considering that in 2014 alone, more than 28,000 people died of opioid poisoning.[52] In addition, it is not totally clear how much of a factor kratom was in the few case reports in which it was implicated as a cause of death. In most of these case reports of possible fatal reactions to kratom, the patients may have had confounding health conditions or may have been using other drugs along with kratom.[1,4,26,40] One of the major problems in evaluating the potential uses and safety of an herbal agent such as kratom is the lack of understanding how substances in kratom may interact with prescription medications, drugs of abuse, or herbal supplements.[1,17]

The lack of regulations and standardization of the production and sale of adulterated kratom products compounds the lack of understanding. Increasing evidence shows that unscrupulous purveyors of adulterated kratom may actually be contaminating their products with potentially toxic drugs.[53-55] Probably the most notorious example of such adulteration involved a product known as *krypton*, which was touted as a highly potent form of kratom. It was sold mainly in Europe and was found to be a factor in at least 9 deaths.[47,56] However, detailed forensic analyses revealed that krypton contained high amounts of the exogenous pharmaceutical agent *O*-desmethyltramadol, which has opioid and neuromodulator activity.[56] Evidently, the exogenous *O*-desmethyltramadol had been added to the plant material. Even though mitragynine was also detected in the products, it was not determined how the 2 substances may have interacted to cause death. The key point is that without some type of standardization and quality control, people who use adulterated kratom products cannot be sure what they are taking. This is obviously a problem that needs to be resolved. Nevertheless, several scientists who have studied kratom indicate that in its pure herbal form, it appears to be relatively benign, especially in comparison with opioids such as hydrocodone, oxycodone, and heroin.[4,26,57]

Discussion

It is readily apparent that kratom is being widely used in the United States, especially for the management of opioid withdrawal and pain. Reports from kratom users and limited basic science and clinical studies suggest that kratom and its constituent compounds may have beneficial pharmacologic effects. However, no well-controlled clinical trials have been done. In response to growing concerns about the safety and addiction/abuse potential of kratom, the DEA is planning to classify kratom and its major mitragynine constituents as Schedule 1 controlled substances despite many patient reports and a few research studies that indicate that kratom is much less harmful than prescription opioids. While it is easy to understand the DEA's perspective, it is also easy to understand the response by kratom users and many in the kratom research community.

One point that is very clear is that these key issues can only be resolved through additional research. However, many experienced kratom researchers have expressed concern that the DEA's plan to move kratom to Schedule 1 will almost certainly make it more difficult for investigators in the United States to address these issues.[58] In this regard, the legal situation with kratom is similar to what has happened with so called "medical marijuana," in which federal policies, including its classification as a Schedule 1 substance, have impeded research.[59] Many institutions and government agencies are reluctant to fund research on Schedule 1 substances. In addition, many practical issues complicate research on herbal products such as kratom. For example, after the publication of our review in 2012,[1] one of the coauthors, Shridhar Andurkar, PhD, and I were planning on conducting basic research on the pharmacologic actions of kratom. With Dr Andurkar's experience using animal models of opioid dependence and withdrawal, we hoped to develop a study to determine whether kratom could suppress symptoms of opioid withdrawal. However,

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we soon realized that this would not be an easy issue to address. Which kratom product would we evaluate? How would we confirm that the product was actually kratom? Resolving that issue would necessitate evaluation by a botanist. How would the product be standardized for activity when it contains a mixture of active compounds? One solution might be to focus on specific chemicals isolated from kratom, but then we would not be able to determine how all of the many active constituents in kratom might interact to produce effects that could differ from those of the individual constituents. Another major issue was how we would administer a plant material such as kratom to laboratory animals in a way that would naturally mimic human consumption.

Conclusion

The only way kratom can be unequivocally studied is through well-controlled clinical trials in humans. Who would fund this type of study? Given that kratom is a tree, would pharmaceutical companies support such work? Would institutional review boards be reluctant to approve trials for a schedule 1 substance? Even though I have no answers to these complex questions, it is my sincere hope that this commentary will facilitate an informed discussion about kratom and foster the necessary research to resolve questions about the safety and utility of kratom in the management of opioid withdrawal and pain. If kratom contains pharmacologically active compounds (which it clearly does), it would certainly have potential toxicities. After evaluating the literature, I can reach no other conclusion than, in pure herbal form, when taken at moderate doses of less than 10 to 15 g, pure leaf kratom appears to be relatively benign in the vast majority of users. Without reported evidence, however, it would not be appropriate for physicians to recommend kratom for their patients. That said, physicians should be aware that their patients may be using kratom.

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Kratom Supporters Rally at White House

September 13, 2016

By Pat Anson, Editor

Hundreds of protestors chanting “kratom saves lives” and “I am kratom” rallied in front of the White House today, hoping to turn their passion for an herb into a movement that stops the Drug Enforcement Administration from making kratom illegal.

“This stuff saved my life. It gave me my life back,” said one protestor.

Kratom comes from the leaves of a tree that grows in southeast Asia, where it has been used for centuries as a natural medicine. In recent years, kratom has grown in popularity in the United States, where it is made into teas and supplements as a treatment for pain, depression, anxiety and addiction.

IMAGE COURTESY AMERICAN KRATOM ASSN.

All of that may change on September 30th, when the DEA plans to schedule the two main active ingredients in kratom as Schedule I controlled substances -- alongside heroin and LSD. That would effectively make the sale and possession of kratom a felony.

Under its emergency scheduling order, the DEA invited no public comment and held no public hearings.

“Stop this ban immediately. You’re trying to protect your jobs. You’re not trying to save Americans,” said Ryan Connor, a military veteran who lost a

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sister to a heroin overdose. “If you take away this herb, more and more people are going to die."

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Connor said he uses kratom to treat his own opioid addiction.

“I’ve been on every opioid under the sun. I was on Suboxone. I was told it was a cure for addiction, but it did not cure my addiction. In fact, it made it worse. I used kratom to get off Suboxone. It was painless. I had zero side effects from it. And I think as Americans we have the right to choose our health over getting poisoned by pharmaceuticals,” Connor said.

In a notice published in the Federal Register, the DEA said an emergency scheduling of kratom was necessary because it has no approved medical use. The DEA claimed the herb was being used recreationally for its "psychoactive effects" and as a substitute for heroin.

The Centers for Disease Control and Prevention also **issued a report last month** calling kratom "an emerging public health threat." The agency said there were 660 calls to U.S. poison control centers about kratom in the last six years. About 8 percent of the calls involved a life threatening condition. One death was reported.

COURTESY PATTI BELMONT

Kratom supporters say the death was more likely caused by prescription drugs and that kratom actually saves lives.

“It changed my life. It rescued me from a very severe addiction to narcotics. It took me out of a home and bed-bound existence. It gave me the energy and pain control that I needed,” said Susan Ash, who founded the **American Kratom Association**, which organized the rally outside the White House.

“We want a regular scheduling process that involves public comment and the best available science, and not just a note from the CDC that said they got all of 660 calls to poison control when they’re getting three to four million calls a year. How do 660 calls make an emerging public health threat?”

Kratom supporters have gotten over 120,000 signatures on an online petition asking the Obama administration to stop the DEA from scheduling kratom as a Schedule I substance. Under its "We the People" petition rules, the administration promises to "take action" on a petition within 60 days if supporters are able to gather at least 100,000 signatures.

According to the website **whpetitions.info**, the average response time for a successful White House petition is well over 100 days – not 60 days. Six petitions -- including the kratom petition -- are currently waiting for a response.

Meanwhile, the **Center for Regulatory Effectiveness (CRE)**, a government watchdog group, has asked the DEA to postpone the scheduling of kratom.

In a September 12 letter to acting DEA Administrator Charles Rosenberg, a CRE official pointed out that the National Institutes of Health has conducted research to explore the therapeutic value of kratom as a treatment for chronic pain and substance abuse.

“The research was so well conducted and received by the scientific community that the aforementioned institutions applied for a patent. How much more additional evidence is needed to demonstrate that the DEA has acted arbitrarily in issuing a ban on kratom?” asked Jim Tozzi, a member of the CRE Board of Advisors.

“In short, without going through a notice and comment process, DEA is obviating another agency’s research that was conducted with appropriated funds. With its action, DEA is also obviating the progress and promise of kratom research to boosting the American bio-sciences industry.”

Tozzi’s letter said the DEA’s “rush to judgement” may have violated the federal Data Information Quality Act and was a “clear and flagrant abuse of discretion.”

He asked the DEA to extend the effective date for scheduling kratom to July 1, 2017, to allow for public comment and a peer review of the science behind the agency’s decision.

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New Hope for Addicts

JANUARY 25, 2013 BY **BARBARA LAGO**

OXFORD, Miss. – It doesn’t take a rocket scientist to quickly grasp what a University of Mississippi professor’s research could mean to the millions of people addicted to hardcore narcotics such as heroin, cocaine, methamphetamine and morphine.

School of Pharmacy faculty member Christopher R. McCurdy has made it his mission to find and develop compounds to unlock the shackles that bind people to addictive drugs.

“A lot of people who become addicted to methamphetamine, cocaine or even heroin truly want to quit,” McCurdy said. “They begin with recreational use and don’t think they will become addicted, but (they) soon get to the point where they almost must take the drug to survive, because withdrawal is so intense.”

Making withdrawal more endurable – and therefore, cessation more likely – is the goal of several projects in McCurdy’s medicinal chemistry laboratory. Among them is a National Institutes of Health Centers of Biomedical Research Excellence-funded study of kratom, a botanical mixture derived from *Mitragyna speciosa*, a treelike plant native to Southeast Asia. (COBRE grants are awarded by the NIH’s National Institute of General Medical Sciences through its Institutional Development Award, or IDeA, program, which builds research capabilities in states that historically have had low levels of NIH funding.)

“In Southeast Asia, kratom has long been used for coughs, diarrhea, muscle aches and pain,” McCurdy said. “It is also used as a replacement for opium when opium isn’t available and has been used to wean people off (that narcotic).”

McCurdy and his colleagues made a tea from *Mitragyna* leaves, freeze-dried it and tested it in mice habituated to morphine. Results indicate the tea has some undesirable side effects but that modifications eliminate them and show great promise.

Taking the work a step further, the group isolated the plant’s most abundant alkaloid, mitragynine, and tested the pure compound. Results indicate this compound’s activity is superior to methadone in the mouse withdrawal assay and that carefully created chemical variations may provide an alternative to methadone in treating addictions to opiates.

“Mitragynine completely blocked all withdrawal symptoms and could provide a remarkable step-down-like treatment for people addicted to hardcore narcotics such as morphine, oxycodone or heroin,” McCurdy said. “The compound has been known for years, but we’re working to come up with an improved synthetic analog or a better formulation of the tea for testing in humans.”

Collaborating on the study is Dr. Edward W. Boyer, professor of emergency medicine and director of medical toxicology at the University of Massachusetts School of Medicine.

“Dr. Boyer is an opium treatment specialist and, through an anonymous chat room, asked kratom users how much they used, how often they used and whether they had any withdrawal symptoms,” McCurdy said. “That information helped us determine dosages and frequencies for our animal studies.”

Despite the U.S. Drug Enforcement Administration listing kratom as a “drug of concern” because of its

Campus Briefs

JULY 6, 2017 BY **STAFF REPORT**

OXFORD, Miss. – The University of Mississippi announced the recommendations it will be implementing from the Chancellor’s Advisory Committee on History and Context. The communication outlining the accepted recommendations as well as the committee’s final report can be accessed at context.OleMiss.edu. Chancellor Jeffrey Vitter established the CACHC in summer 2016 to address Recommendation 5 of

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MAY 20, 2017 BY **BRETT BAREFOOT**

OXFORD, Miss. – Gifts to a new scholarship endowment in the University of Mississippi School of Business Administration will honor the life of the late Robert Julian Allen III, a successful entrepreneur who had a strong interest in giving young people opportunities to manage or own a business. The Robert Julian Allen III Memorial Scholarship

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abuse potential and stating there is no legitimate medical use for it in this country, several million Americans purchase kratom on the Internet to self-manage chronic pain and/or opioid withdrawal, and some are ending up in emergency rooms. After one who had been using kratom four times a day for

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HEALTH

Should Kratom Use Be Legal?

Thailand is considering legalizing kratom as a safer alternative for meth addicts, and U.S. researchers are studying its potential to help opiate abusers kick the habit without withdrawal side effects. Is that a good thing?

By Larry Greenemeier on September 30, 2013

Credit: Courtesy of Uomo vitruviano, via Wikimedia Commons

The leaves of the herb kratom (*Mitragyna speciosa*), a native of Southeast Asia in the coffee family, are used to relieve pain and improve mood as an opiate substitute and stimulant. The herb is also combined with cough syrup to make a popular beverage in Thailand called “4x100.” Because of its psychoactive properties, however, kratom is illegal in Thailand, Australia, Myanmar (Burma) and Malaysia. The U.S. Drug Enforcement Administration lists kratom as a “drug of concern” because of its abuse potential, stating it has no legitimate medical use. The state of Indiana has banned kratom consumption outright.

Now, looking to control its population’s growing dependence on methamphetamines, Thailand is attempting to legalize kratom, which it had originally banned 70 years ago.

At the same time, researchers are studying kratom's ability to help wean addicts from much stronger drugs, such as heroin and cocaine. Studies show that a compound found in the plant could even serve as the basis for an alternative to methadone in treating addictions to opioids. The moves are just the latest step in kratom's strange journey from home-brewed stimulant to illegal painkiller to, possibly, a withdrawal-free treatment for opioid abuse.

With kratom's legal status under review in Thailand and U.S. researchers delving into the substance's potential to help drug addicts, *Scientific American* spoke with Edward Boyer, a professor of emergency medicine and director of medical toxicology at the University of Massachusetts Medical School. Boyer has worked with Chris McCurdy, a University of Mississippi professor of medicinal chemistry and pharmacology, and others for the past several years to better understand whether kratom use should be stigmatized or celebrated.

[*An edited transcript of the interview follows.*]

How did you become interested in studying kratom?
A few years ago [the National Institutes of Health] wanted me to do a bit of consulting on emerging drugs that people might abuse. I came across kratom while searching online, but didn't think much of it at first. When I mentioned it to the NIH, they suggested I speak with a researcher at the University of Mississippi who was doing work on kratom. [The researcher, McCurdy,] assured me that kratom was fascinating, and he started to go through the science behind it. I decided I needed to look into it further. Talk about chance favoring the prepared mind. I no sooner hung up the phone when a case of kratom abuse popped up at Massachusetts General Hospital.

How did this Mass General patient come to abuse kratom?
He was a [43-year-old] successful software engineer who had been self-medicating for chronic pain [as a result of thoracic outlet syndrome, a group of disorders that occurs when the blood vessels or nerves in the space between the collarbone and the first rib—the thoracic outlet—become compressed, causing pain in the shoulders and neck as well as numbness in the fingers]. He had started with pain pills, then switched to OxyContin, and then moved to Dilaudid, which is a high-potency opioid analgesic. He had gotten to the point where he was injecting himself with 10 milligrams of Dilaudid per day, which is a large dose. His wife found out and demanded that he quit.

He read about kratom online and started making a tea out of it. For the most part, this helped him avoid the opioid withdrawal he had been experiencing. After he started drinking the kratom tea, he also began to notice that he could work longer hours and that he was more attentive to his wife when they would speak. He began experimenting with ways to boost his alertness by adding modafinil [a U.S. Food and Drug Administration–approved stimulant] with his kratom tea. That's when he started to seize and had to be brought to the hospital. I have no idea how that combination of drugs caused a seizure, but that's how he ended up at Mass General Hospital. Nobody there had heard of kratom abuse at the time. [Boyer and several colleagues, including McCurdy, published a case study about this incident in the June 2008 issue of the journal *Addiction*.]

The patient was spending $15,000 annually on kratom, according to your study, which is quite a lot for tea. What happened when he left the hospital and stopped using it?
After his stay at Mass General, he went off kratom cold turkey. The fascinating thing is that his only withdrawal symptom was a runny noise. As for his opioid withdrawal, we learned that kratom blunts that process awfully, awfully well.

Where did your kratom research go from there?
I had a small grant from the NIH's National Institute on Drug Abuse to look at individuals who self-treated chronic pain with opioid analgesics they purchased without prescription on the Internet. This was an extremely restricted population, but it nonetheless measures in the hundreds of thousands of people. About the time I started the study, the DEA and the state boards of pharmacy began shutting down online pharmacies, so sources of pain pills for these hundreds of thousands of people in the United States dried up instantaneously. A number of them switched to kratom.

How many people are using kratom in the U.S.?
I don't know that there's any epidemiology to inform that in an honest way. The typical drug abuse metrics don't exist. But what I can tell you, based on my experience researching emerging drugs of abuse is that it is not difficult to get online.

How does kratom work?
Its pharmacology and toxicology aren't well understood. Mitragynine—the isolated natural product in kratom leaves—binds to the same mu-opioid receptor as morphine, which explains why it treats pain. It's got kappa-opioid receptor activity as well, and it's also got adrenergic activity as well, so you stay alert throughout the day. This would explain why the guy who overdosed described himself as being more attentive. Some opioid medicinal chemists would suggest that kratom

pharmacology might [reduce cravings for opioids] while at the same time providing pain relief. I don't know how realistic that is in humans who take the drug, but that's what some medicinal chemists would seem to suggest.

Kratom also has serotonergic activity, too—it binds with serotonin receptors. So if you want to treat depression, if you want to treat opioid pain, if you want to treat sleepiness, this [compound] really puts it all together.

Overdosing and drug mixing aside, is kratom dangerous?
People are afraid of opioid analgesics because they can lead to respiratory depression [difficulty breathing]. When you overdose on these drugs, your respiratory rate drops to zero. In animal studies where rats were given mitragynine, those rats had no respiratory depression. This opens the possibility of someday developing a pain medication as effective as morphine but without the risk of accidentally overdosing and dying.

What barriers have you run into when trying to study kratom?
I tried to get an NIH grant to study kratom specifically. When I went to the National Institute on Drug Abuse, they said they'd never heard of that drug. When I went to the National Center for Complementary and Alternative Medicine, they said this is a drug of abuse, and we don't fund drug of abuse research. They want drugs that are used therapeutically. [A team led by McCurdy, who confirms that it is difficult to get funding to study kratom, did manage to secure a three-year grant from the NIH Centers of Biomedical Research Excellence to investigate the herb's opioid-like effects.]

So the study of this type of substance falls to academics or pharma companies. Drug companies are the ones who can isolate a particular compound, do chemistry on it, study and modify the structure, figure out its activity relationships, and then create modified molecules for testing. Then you have eventually file for a new drug application with the FDA in order to conduct clinical trials. Based on my experiences, the likelihood of that happening is reasonably small.

Why wouldn't large pharmaceutical companies try to make a blockbuster drug from kratom?
At least one pharma company [Smith, Kline & French, now part of GlaxoSmithKline] was looking at it in the 1960s, but something didn't work for them. Either it wasn't a strong enough analgesic or the solubility was bad or they didn't have a drug delivery system for it. To the state of the art pharmaceutical business thinking in 1960s, this

compound was not sufficient to be brought to market. Of course, now that we have a country with many addicted people dying of respiratory depression, having a drug that can effectively treat your pain with no respiratory depression, I think that's pretty cool. It might be worth a second look for pharma companies.

There are reports that Thailand might legalize kratom to help that country control its meth problem. Could that work?
They can decriminalize kratom until they're blue in the face but the reality is that kratom is indigenous to Thailand—it's readily available and always has been. Yet drug users are still opting for methamphetamines, which are stronger than kratom, not to mention dirt cheap and widely available. I suspect that Thailand is just trying to say that they're doing something about their meth problem, but that it might not be that effective.

Is kratom addictive?
I don't know that there are studies showing animals will compulsively administer kratom, but I know that tolerance develops in animal models. I can tell you the guy in our Mass General case report went from injecting Dilaudid to using [$15,000] worth of kratom per year. That kind of sounds addictive to me. My gut is that, yeah, people can be addicted to it.

What are the dangers posed by kratom use or abuse?
It's just like any other opioid that has abuse liability. Heroin was once marketed as a therapeutic product and later was criminalized. Yet OxyContin [a painkiller with a high risk for abuse] was marketed as a therapeutic but has remained legal. You put the proper safeguards in place and hope that people won't abuse a substance. Speaking as a scientist, a physician and a practicing clinician, I think the fears of adverse events don't mean you stop the scientific discovery process totally.

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AMERICAN KRATOM ASSOCIATION

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Pharmacology of Kratom: An Emerging Botanical Agent With Stimulant, Analgesic and Opioid-Like Effects

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Kratom (*Mitragyna speciosa*) is a plant indigenous to Thailand and Southeast Asia. Kratom leaves produce complex stimulant and opioid-like analgesic effects. In Asia, kratom has been used to stave off fatigue and to manage pain, diarrhea, cough, and opioid withdrawal. Recently, kratom has become widely available in the United States and Europe by means of smoke shops and the Internet. Analyses of the medical literature and select Internet sites indicate that individuals in the United States are increasingly using kratom for the self-management of pain and opioid withdrawal. Kratom contains pharmacologically active constituents, most notably mitragynine and 7-hydroxymitragynine. Kratom is illegal in many countries. Although it is still legal in the United States, the US Drug Enforcement Administration has placed kratom on its "Drugs and Chemicals of Concern" list. Physicians should be aware of the availability, user habits, and health effects of kratom. Further research on the therapeutic uses, toxic effects, and abuse potential of kratom and its constituent compounds are needed.

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Throughout history, humans have used plant-derived materials (often referred to as "herbal" or "botanical" remedies) to treat diseases, cope with the stresses of life, and achieve altered states of awareness. Even with the development of modern pharmaceuticals and medical practices, many people still use herbal remedies either as alternatives to or in conjunction with mainstream medical care. Several years ago, Barnes et al[1] found that more than 30% of US patients had or were using some form of herbal-based remedy. They also noted that the agents were being used primarily for "musculoskeletal or other conditions involving chronic pain."[1]

Even though the efficacies of most of these herbal remedies have yet to be proven in controlled clinical trials, it is clear that such products are being used extensively. Whether they are consumed alone or in combination with prescribed medications, herbal remedies have the potential to cause toxic effects, interact with prescription drugs, and complicate the diagnosis and treatment of disease.[2] At the same time, however, herbal remedies may have substantial therapeutic effects. Some evidence[2] suggests that certain herbal products may, in fact, have therapeutic actions that are equivalent to those of modern pharmaceuticals. Moreover, research on the effects of herbal supplements and their active constituents may provide insight that could lead to the development of new and more effective therapeutic agents.

Given the extensive use of herbal remedies, it is important that physicians and other health care professionals have some knowledge of their attendant issues. This topic is especially relevant to osteopathic physicians because the tenets of osteopathic medicine focus on a unified approach to patient care, musculoskeletal health, and self-healing.[3] Osteopathic physicians should be familiar with common herbal remedies that their patients may be using. One herbal remedy that has been receiving increased public attention in recent years is kratom.[4] In the present article, we discuss current patterns of usage, basic pharmacology, legal standing, and medicinal potential of kratom.

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Background

The term *kratom* refers to a group of tree-like plants belonging to the Mitragyna genus of the Rubiaceae family.[4-9] Other members of the Rubiaceae family include the coffee and gardenia plants. From a medical perspective, the most important species of kratom is *Mitragyna speciosa*, which is indigenous to Thailand and surrounding countries in Southeast Asia.[7] Images of a kratom plant and a kratom leaf are shown in *Figure 1*.

Kratom has been widely used in Southeast Asia for hundreds of years.[5,6] In Thailand, kratom use typically involves ingestion of the plant's raw leaves or consumption of teas that are brewed or steeped from the leaves.[4,6,9] Kratom leaves are used for their complex, dose-dependent pharmacologic effects.[4,6,9-12] Low to moderate doses (1-5 g) of the leaves reportedly produce mild stimulant effects that enable workers to stave off fatigue.[6,9-11,13] Moderate to high doses (5-15 g) are reported to have opioid-like effects.[6,9-11,13] At these doses, kratom has been used for the management of pain, diarrhea, and opioid withdrawal symptoms, as well as for its properties as a euphoriant.[5,6,9-11,14] Very high doses (>15 g) of kratom tend to be quite sedating and can induce stupor, mimicking opioid effects.[4,5,9]

Growth of Kratom Use in the West

Recent Research

Despite its long history and widespread use in Southeast Asia, kratom has only recently begun to receive attention and be used as an herbal remedy in the West. The emergence of kratom as a product or drug of interest in the United States is evident from the results of our literature search. Our search of the US National Library of Medicine's PubMed database in February 2012, using the keyword "kratom," yielded a total of 35 published articles and reviews. Of those, 30 (86%) were published in or after 2004, 4 (11%) were published between 1988 and 1997, and 1 (3%) was published in 1975. Another PubMed search, using the keywords "*Mitragyna speciosa*," yielded a total of 65 published articles. Of those, 49 (75%) were published within the past 10 years.

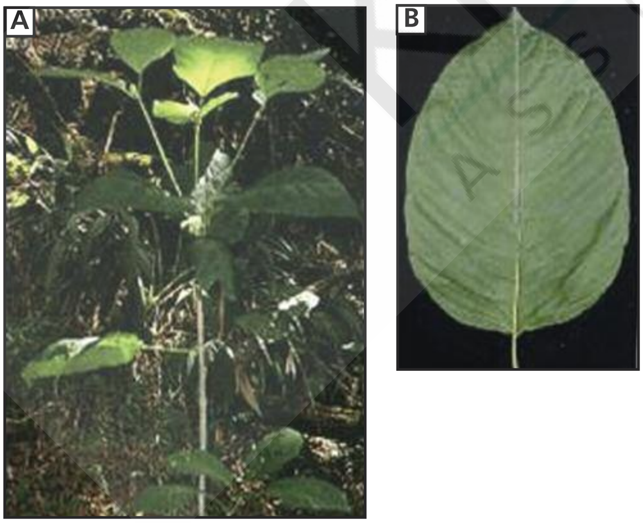

Figure 1. *Images of a kratom plant (A) and a kratom leaf (B). Images were obtained from the US Drug Enforcement Administration Web site.*[4,29]

In addition to these general trends in the number of publications on kratom, we found that an increasing number of reports of adverse effects resulting from the use of kratom have been published.15-19 Recent news reports have highlighted the increasing level of kratom use, particularly among college-aged populations.[20,21] Moreover, published studies indicate that vast numbers of online vendors and general information Web sites for kratom have appeared in the past few years, suggesting that there is a substantial demand for kratom products.[22,23]

Increased Internet Presence

In February 2012, we also conducted an Internet search using the Google search engine. A search for the keyword "kratom" found more than 2 million results. Of the first 100 Web sites listed in the search results, 78 were primarily focused on the sale of kratom, while 22 Web sites primarily focused on disseminating information about kratom through the use of discussion boards. We want to strongly emphasize that the scientific validity of the claims and anecdotes reported on these Web sites has not been substantiated. Moreover, for the purpose of the present review, we did not believe it was appropriate to cite all sources of anecdotal information. However, we did find 3 Web sites to be particularly informative: Erowid.org[24]; Sagewisdom .org[25]; and WebMD.com[26]. These Web sites contain a variety of information including the drug's uses and effects, discussions of individuals' personal experiences, and adverse reactions when using kratom. Some of the Web sites[24,25] even describe the biology of *Mitragyna speciosa*, including optimal methods and conditions for growing. In addition, an analysis by León et al[7] suggests cultivation exists here in the United States. It is also important to note that much of the content of these Web sites clearly indicates that kratom is being used for medicinal purposes. Although some sites[24-26] portray users of kratom as recreational drug users, many posts on kratom blogs are from patients dealing with pain management issues.[24-26] In some cases,[24-26] individuals report finding relief of various types of pain with kratom use. In addition, recent publications have highlighted the use of kratom products for the self-management of opioid withdrawal symptoms.[20,27] Although the anecdotal claims reported on the aforementioned Web sites and publications have not been substantiated, their existence indicates that kratom is being used in these contexts.

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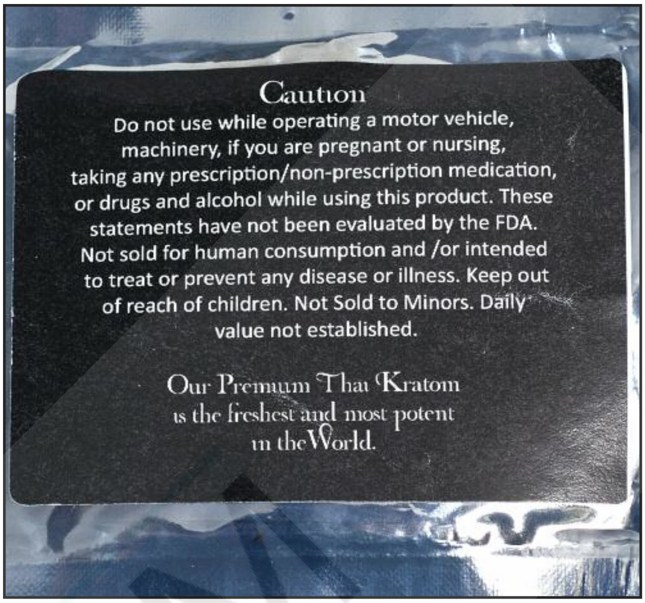
Legal Status and Availability

Although the findings of our literature and Internet searches strongly suggest a marked increase in kratom use in the United States and Europe, kratom still appears to be somewhat of an "underground phenomenon." During our searches of the literature and the internet, we found no evidence that kratom is currently marketed by any of the large nutritional supplement chain stores in the United States. However, a wide variety of kratom products—including raw leaves, capsules, tablets, and concentrated extracts—are readily available from Internet-based suppliers.[20,21] In addition, these products are often sold in specialty stores commonly known as "head shops" or "smoke shops." In February 2012, our own informal in-person and telephone survey of 5 smoke shops in the metropolitan Chicago area revealed that purported kratom products were available in all of them. *Figure 2* and *Figure 3* show images of several kratom products (ie, chopped leaves, capsules, and pressed tablets) that were legally purchased at a smoke shop in suburban Chicago.

From a legal standpoint, kratom is regulated as an herbal product under US law and US Food and Drug Administration and US Drug Enforcement Administration (DEA) policies. As of this writing, *Mitragyna speciosa* (kratom) is not prohibited by the Controlled Substances Act[28] and is considered a legal substance in the United States. However, the DEA's December 2010 version of the Drugs and Chemicals of Concern list states that "there is no legitimate medical use for kratom in the U.S."[29] Therefore, it cannot legally be advertised as a remedy for any medical condition.



Caution

Do not use while operating a motor vehicle, machinery, if you are pregnant or nursing, taking any prescription/non-prescription medication, or drugs and alcohol while using this product. These statements have not been evaluated by the FDA. Not sold for human consumption and /or intended to treat or prevent any disease or illness. Keep out of reach of children. Not Sold to Minors. Daily value not established.

Our Premium Thai Kratom is the freshest and most potent in the World.

Figure 3. *Warning label on the back of a package of kratom capsules.*

Pharmacology of Kratom

Chemistry and Pharmacognosy

As the use of kratom in the West has grown during the past 15 years,[4,20,23,30] there have been increased efforts to identify and characterize the active pharmacologic agents that mediate the effects of kratom in the body. Thus far, more than 20 active compounds have been isolated from kratom, and considerable evidence shows that these compounds do, in fact, have major pharmacologic effects.[30,31] Various aspects of the medicinal chemistry and pharmacognosy of kratom have recently been reviewed by Adkins et al.[30] Accordingly, only a few key points regarding these topics will be considered in the present article. The *Table* shows the chemical structures and summarizes the major pharmacologic actions of some of the kratom-derived compounds that have been studied most extensively. The most extensively-characterized of kratom's active pharmacologic

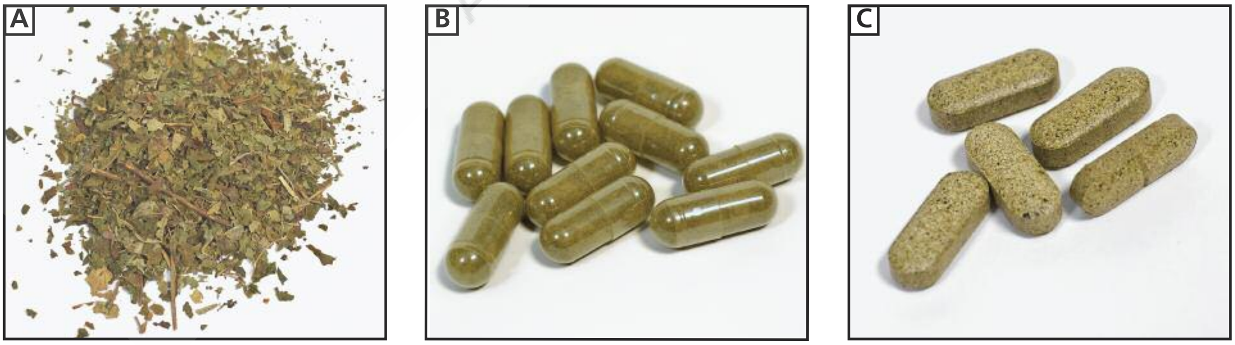


Figure 2. *Images of kratom products purchased at a "smoke shop" in suburban Chicago. The images show chopped leaves (A), which are typically brewed into "kratom tea", capsules containing finely chopped leaves (B), and compressed tablets containing leaves or resin (C).*

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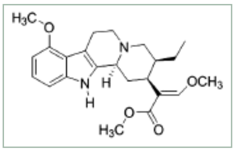
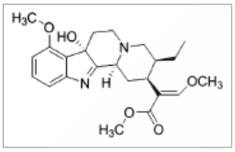
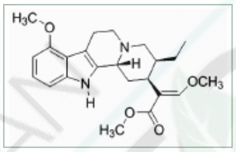
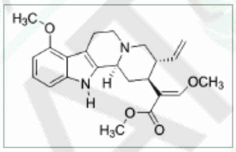
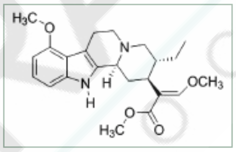
Table.
Structures and Pharmacologic Activities of Compounds Isolated From Kratom

Compound	Structure	Pharmacology
Mitragynine[30,33,34,39,40,44]		Structurally similar to yohimbine Activity on μ, δ, and κ receptors Main activity on μ receptors creating opiate and analgesic effects and physical dependence Inhibits radioligand binding at central nervous system receptors Activates descending noradrenergic and serotonergic pathways in spinal cord Stimulates postsynaptic α_2-adrenergic receptors Blocks stimulation of 5-hydroxytryptamine$_{2A}$ receptors
7-Hydroxymitragynine[30,33,34,39,40,44]		13- and 46-fold higher potency than morphine and mitragynine, respectively Potency and quick-acting characteristics may be caused by introduction of –OH group on C7 position Induces clinically significant antinociceptive responses in a dose-dependent manner
Speciociliatine[30,44]		C3 stereoisomer of mitragynine Inhibits twitch contraction in naloxone-insensitive manner May inhibit acetylcholine release from presynaptic nerve through means other than opioid receptor stimulation
Paynantheine[40,44]		Inhibits twitch contraction in naloxone-insensitive manner Inhibits muscarine receptors on ileal smooth muscle
Speciogynine[40,44]		Inhibits twitch contraction in naloxone-insensitive manner Inhibits muscarine receptors in ileal smooth muscle

agents have been the mitragynine analogs.[30] These agents contain an indole ring and are, in some respects, structurally similar to yohimbine.[30] These agents have been shown to produce a wide variety of pharmacologic effects, both in vivo and in vitro.[30] In the following sections, we will consider the importance of these compounds as they relate to the primary pharmacologic effects of kratom, particularly analgesia and the ability to suppress symptoms of opioid withdrawal.

Analgesic and Opioid-Like Effects

In Southeast Asia, kratom has long been used for the management of pain and opium withdrawal.[6,9-11,14] In the West, kratom is increasingly being used by individuals for the self-management of pain or withdrawal from opioid drugs such as heroin and prescription pain relievers.[20,27] It is these aspects of kratom pharmacology that have received the most scientific attention. Although to our knowledge, no well-controlled clinical studies on the effects of kratom on humans have been published, there is evidence[30-38] that kratom, kratom extracts, and molecules isolated from kratom can alleviate various forms of pain in animal models. Studies have used a variety of methods including hot plate,[35,37,39] tail flick,[32,39] writhing,[37,38] and pressure/inflammation[35,38] tests in mice[32,35,38,39] and rats,[35,37] as well as more elaborate tests in dogs and cats.[35] In addition, a variety of chemical compounds have been isolated from kratom and shown to exhibit opioid-like activity on smooth muscle systems[31,33,34] and in ligand-binding studies.[39,40] Most notably, many of the central nervous system and peripheral effects of these kratom-derived substances are sensitive to inhibition by opioid antagonists.[31-34,39-41]

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Most of the opioid-like activity of kratom has been attributed to the presence of the indole alkaloids, mitragynine and 7-hydroxymitragynine. Both compounds have been shown to have analgesic and antinociceptive effects in animals, although 7-hydroxymitragynime is more potent.[30,32,40] These agents also produce opioid-like effects on organs such as the intestines and male internal genitalia.[33,34] Moreover, when they are given to animals for 5 days or longer, both compounds produce a state of physical dependence, with withdrawal symptoms that resemble those of opioid withdrawal.[31,32,41] In addition, ligand-binding studies and those using opioid antagonists indicate that these effects are largely mediated by means of actions on μ- and δ-type opioid receptors.[30,31,33] Along with these various central nervous system effects, kratom also appears to have anti-inflammatory activity.[38] Utar et al[42] recently found that mitragynine can inhibit lipopolysaccharide-stimulated cyclooxygenase-2 expression and prostaglandin E2 production. In addition to direct mediation by means of opioid receptors, the antinociceptive effects of mitragynine appear to involve the activation of descending noradrenergic and serotonergic pathways in the spinal cord.[43] Additionally, animal studies have shown that mitragynine may stimulate postsynaptic α_2-adrenergic receptors and possibly even block 5-hydroxytryptamine$_{2A}$ receptors.[33] Although kratom contains lower levels of 7-hydroxymitragynine than mitragynine, it has been suggested that 7-hydroxymitragynine is more potent and has better oral bioavailability and blood brain-barrier penetration than mitragynine,[30,40] making it the predominant mediator of analgesic effects of kratom in the body.

Other compounds that have been isolated from kratom and implicated in some of its effects include speciociliatine, speciogynine, and paynatheine.[30,40] These compounds have been shown to modulate intestinal smooth muscle function and behavioral response in animals.[33,34,40,44] However, these effects were not inhibited by the opioid receptor antagonist naloxone, suggesting that they involve opioid-independent mechanisms.[40,44] It remains to be determined how these compounds may contribute to the overall actions of kratom in vivo.

Subjective Effects

In spite of the fact that kratom has been widely touted and used as a "legal opioid,"[23,31] few scientific studies have addressed the psychoactive properties of kratom.[6,9,11,12] Most of the available information is based on anecdotal reports and patient experiences. The general subjective effects of kratom have been summarized in various reviews.[6,9,12,30] In addition, many individuals have posted descriptions of their personal kratom experiences on Web sites such as Erowid, Sagewisdom, and WebMD.[24-26] As noted previously, kratom produces an unusual combination of stimulant- and opioid-like effects. These effects are highly dependent on the dose of kratom and can vary markedly from one individual to another. Low to moderate doses (1-5 g of raw leaves) usually produce a mild stimulant effect that most individuals perceive as pleasant but not as intense as those of amphetamine-like drugs.[24,25] Some individuals, however, report that these low-dose effects are mainly characterized by an unpleasant sense of anxiety and internal agitation.[24-26] It is noteworthy that those who have used kratom products for pain management tend to view the stimulant effects of kratom as being more desirable than the sedative effects of traditional opioids.[24-26]

Opioid-like effects, such as analgesia, constipation, euphoria, and sedation are typically associated with the use of moderate-high doses of kratom (5-15 g). As with the lower-dose effects, the higher-dose effects may be either euphoric or dysphoric, depending on the individual. Of note, the euphoric effects of kratom generally tend to be less intense than those of opium and opioid drugs.[6,10,11,25] Nevertheless, kratom is still sought by drug users.

Toxic Effects and Untoward Reactions

During the past 3 years, there have been an increasing number of case reports[15,17,29] describing unusual adverse reactions in patients who had been using kratom or kratom-based products. The acute adverse effects of kratom experienced by many users appear to be a direct result of kratom's stimulant and opioid activities.[6,9,11,30,31] Stimulant effects may manifest themselves in some individuals as anxiety, irritability, and increased aggression. Opioid-like effects include sedation, nausea, constipation, and itching. Again, these effects appear to be dose dependent and to vary markedly from one individual to another. Chronic, high-dose usage has been associated with several unusual effects. Hyperpigmentation of the cheeks, tremor, anorexia, weight loss, and psychosis have been observed in individuals with long-term addiction.[9] Reports of serious toxic effects are rare and have usually involved the use of relatively high doses of kratom (>15 g).[9,17,45,46] Of particular concern, there have been several recent reports of seizures occurring in individuals who have used high doses of kratom, either alone or in combination with other drugs, such as modafinil.[17,22,45] Kapp et al[15] recently described a case of intrahepatic cholestasis in a chronic user of kratom.

It is important to note that in each of these case reports, the patients may have had confounding health conditions, may have been using other drugs along with kratom, or both. One of the major problems in evaluating the potential uses and safety of an herbal agent such as kratom is the lack of understanding of how substances in kratom may interact with prescription medications, drugs of abuse, or

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even other herbal supplements. This issue is compounded by the relative lack of regulations and standardization related to the production and sale of kratom. These potential hazards were highlighted in several case reports of deaths resulting from the use of a kratom-based product known as "Krypton".[16,47] This agent, which was touted as a very potent form of kratom, had been marketed in Sweden. During the past 5 years, there have been reports of 9 deaths related to the use of Krypton.[16] In a case series by Kronstad et al,[16] subsequent forensic studies revealed that Krypton contained high amounts of the exogenous pharmaceutical agent *O*-desmethyltramadol, which has opioid and neuromodulator activity. Evidently, the exogenous *O*-desmethyltramadol had been added to the plant material. Even though mitragynine was also detected in the products, it was not determined how the 2 substances may have interacted to cause death. Another recent report[48] described a fatal reaction that appeared to be associated with the use of a combination of propylhexedrine—an α agonist and an amphetamine-like stimulant—and mitragynine. This latter case highlights the fact that extracts and tinctures containing purified mitragynine, 7-hydroxymitragynine, and 7-acetoxymitragynine have become available for purchase by means of the Internet. These sources can easily be found by conducting an Internet search using the term "mitragynine purchase." The possibility that these highly concentrated mitragynine alkaloid extracts could be used in conjunction with other psychoactive drugs (eg, alcohol, sedatives, opioids, stimulants, cannabinoids) raises the potential for serious drug interactions.

Kratom Abuse, Dependence, and Addiction Potential

A large number of Internet posts refer to the use of kratom as a euphoriant or "legal opioid."[23-26] A major question that remains unanswered is, "How addictive is kratom?" Although many anecdotal reports suggest that it may be less addictive than classical opioids, there are also numerous reports that, in some individuals, it may be highly addictive. For example, in Southeast Asia, it has long been recognized that individuals will seek out and abuse kratom for its euphoric and mind-altering effects and that chronic users can become tolerant of, physically dependent on, and addicted to kratom.[9,10] Kratom addiction is considered such a problem that many Southeast Asian countries have outlawed the use of kratom.[9,10]

As kratom use has expanded to Europe and the United States, there have been increasing reports of individuals becoming physically dependent on or addicted to kratom.[22,30,31,45,46] Most published studies are case reports[22,31,45,46] of heavy, compulsive users of kratom. In each case, the individual exhibited substantial tolerance to the effects of kratom and showed overt symptoms of withdrawal when kratom use was stopped. The symptoms of withdrawal were similar to those from traditional opioids and included irritability, dysphoria, nausea, hypertension, insomnia, yawning, rhinorrhea, myalgia, diarrhea, and arthralgias. In a recent report, McWhirter and Morris[45] described the use of an opioid agonist (dihydrocodeine) and an α-adrenergic antagonist (lofexidine) to successfully manage symptoms of withdrawal in an individual who was addicted to kratom.

Drug Screening and Analyses

Kratom and kratom-derived compounds such as mitragynine and 7-hydroxymitragynine are not detected in most routine drug testing or screening procedures.[49] Although various tests for kratom-derived compounds have been developed,[49] they are not yet widely available for general use. Moreover, there are still some controversies regarding the designation of drug-level cutoff points for defining the tests.[49] The analytical and forensic aspects of kratom toxicology have been summarized in a review by Philipp et al.[49]

Conclusion

Evidence suggests that kratom is being used extensively for both medical and nonmedical purposes. Recent studies have shown that kratom contains a variety of active compounds that produce major pharmacologic effects at opioid and other receptors. Kratom and kratom-derived drugs may potentially be used for the management of pain, opioid withdrawal symptoms, and other clinical problems. At the same time, serious questions remain regarding the potential toxic effects and the abuse and addiction potential of kratom. This issue is further confounded by the lack of quality control and standardization in the production and sale of kratom products. The possibilities of kratom products being adulterated or interacting with other drugs are also serious concerns. Until these issues are resolved, it would not be appropriate for physicians to recommend kratom for the treatment of patients. Nevertheless, physicians need to be aware that patients may use kratom or kratom-based products on their own. Further studies to clarify the efficacy, safety, and addiction potential of kratom are needed.

Acknowledgments

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(continued)

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A SURVEY OF ER/TRAUMA HEALTH CARE PROFESSIONALS CONDUCTED FOR THE AMERICAN KRATOM ASSOCIATION

Tuesday, November 29, 2016

Powered by SurveyMonkey®

105

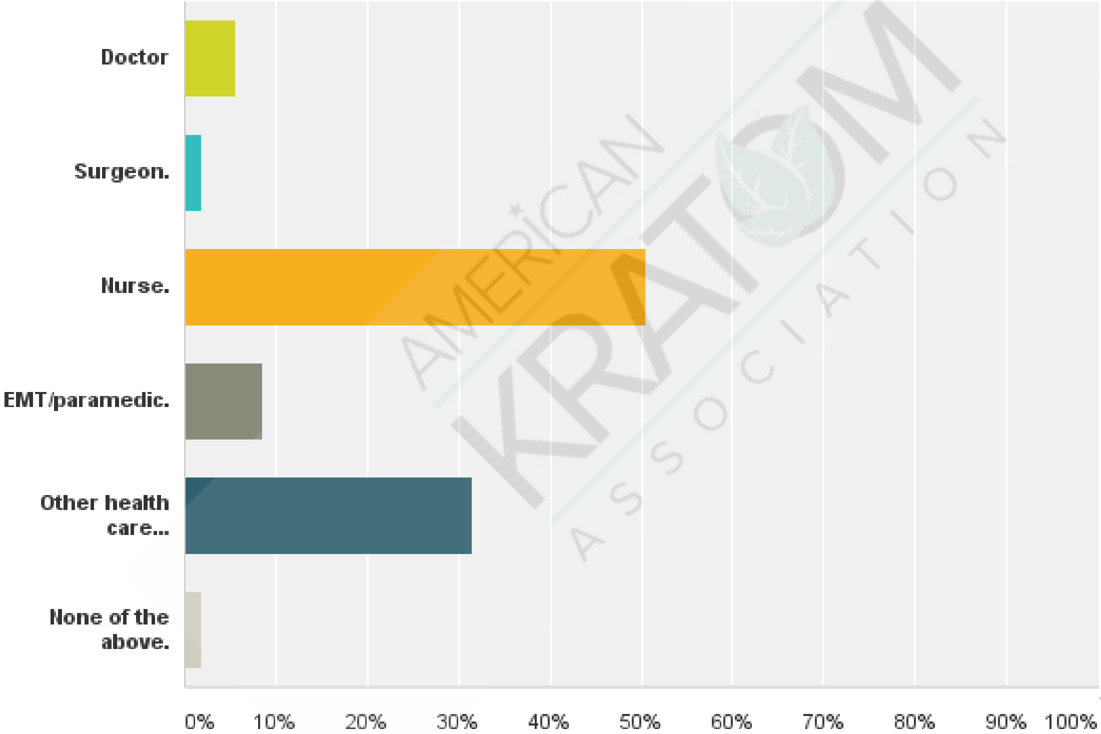
Total Responses

Survey Period: Wednesday, November 23, 2016-Monday, November 24, 2016

Complete Responses: 104

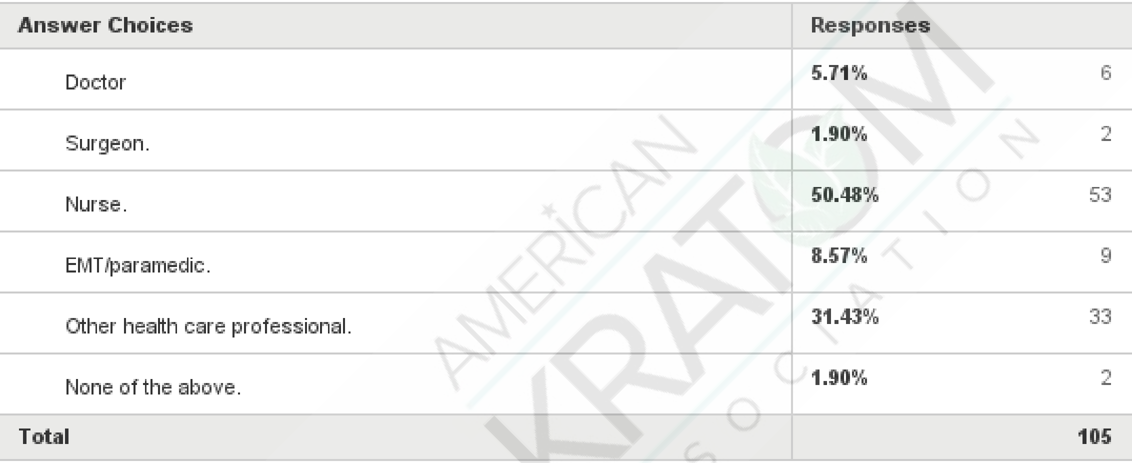
Q1: Which of the following best describes you?

Answered: 105 Skipped: 0



Q1: Which of the following best describes you?

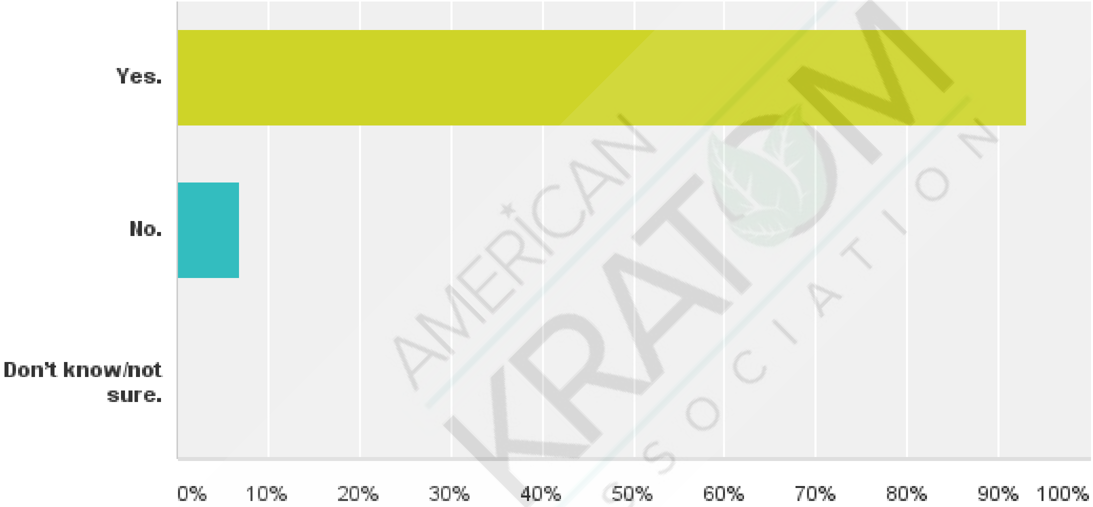
Answered: 105   Skipped: 0



Answer Choices	Responses	
Doctor	**5.71%**	6
Surgeon.	**1.90%**	2
Nurse.	**50.48%**	53
EMT/paramedic.	**8.57%**	9
Other health care professional.	**31.43%**	33
None of the above.	**1.90%**	2
Total		**105**

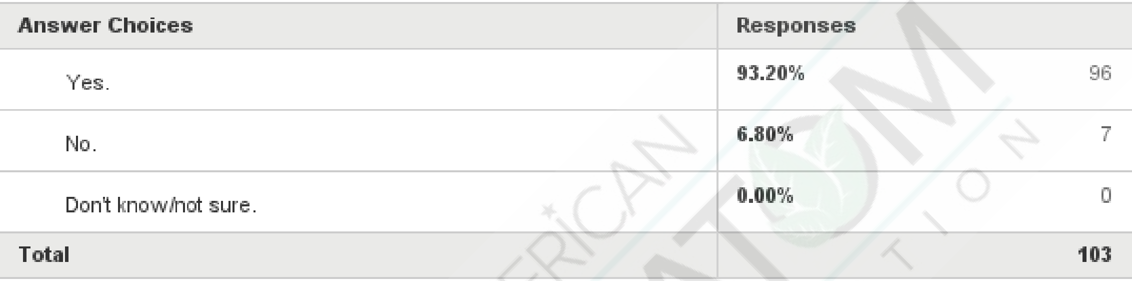
Q2: Have you heard of the herb kratom?

Answered: 103   Skipped: 2



Q2: Have you heard of the herb kratom?

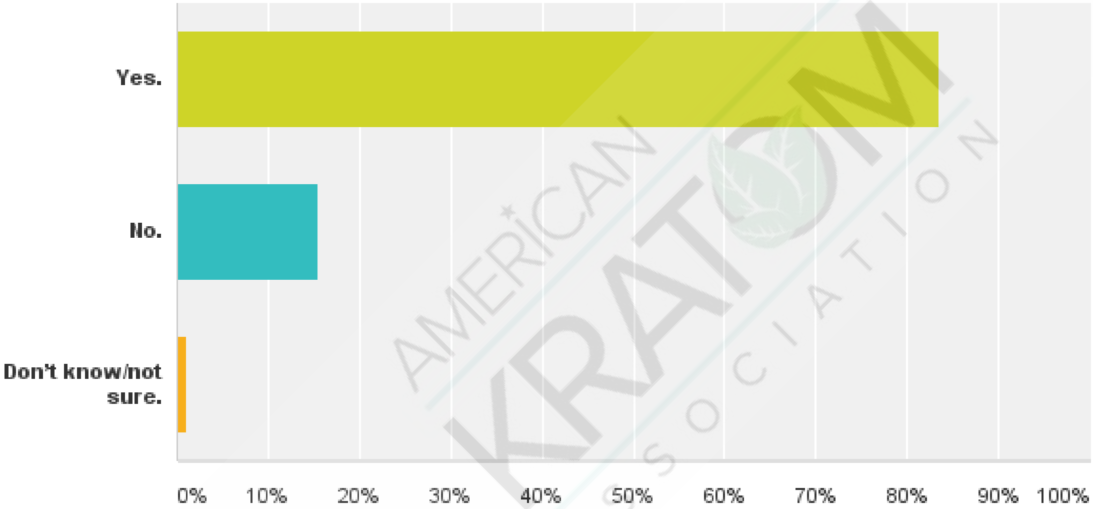
Answered: 103   Skipped: 2



Answer Choices	Responses	
Yes.	**93.20%**	96
No.	**6.80%**	7
Don't know/not sure.	**0.00%**	0
Total		**103**

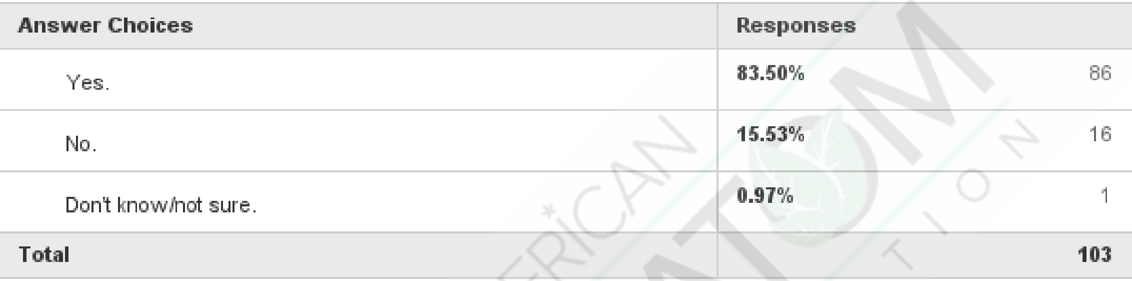
Q3: Have you ever consumed kratom personally?

Answered: 103 Skipped: 2



Q3: Have you ever consumed kratom personally?

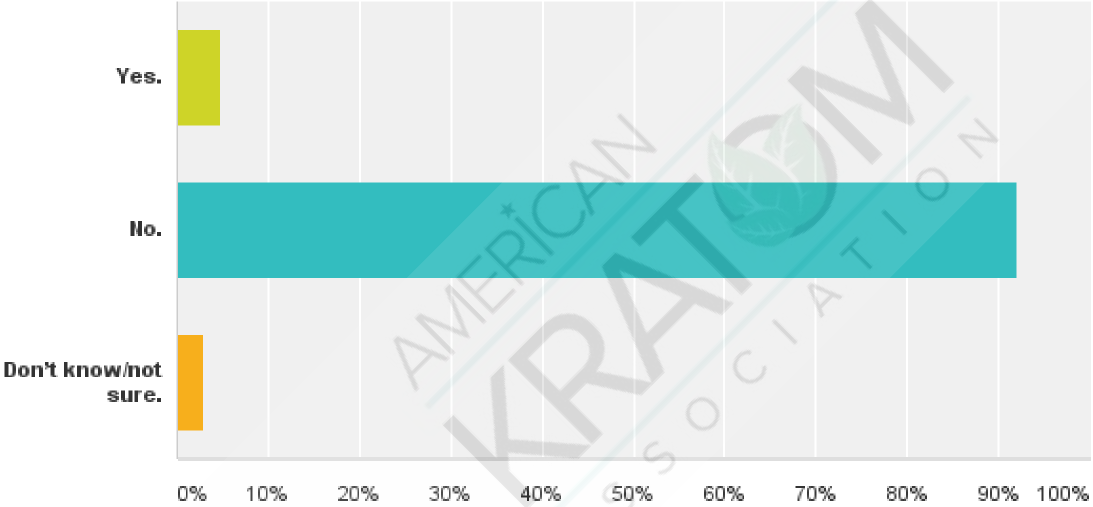
Answered: 103 Skipped: 2



Answer Choices	Responses	
Yes.	83.50%	86
No.	15.53%	16
Don't know/not sure.	0.97%	1
Total		**103**

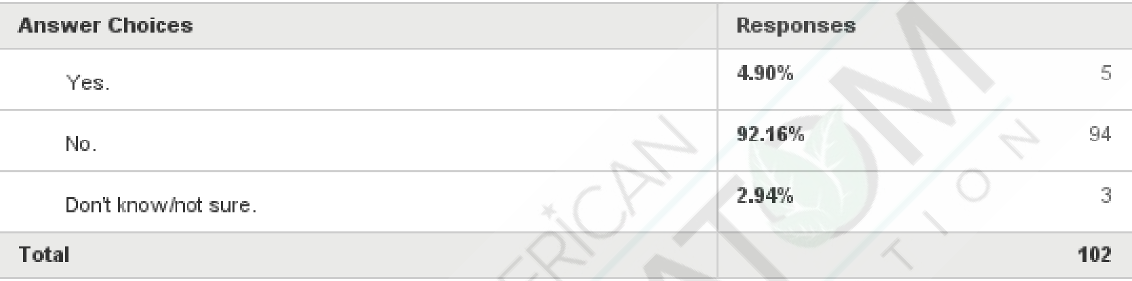
Q4: Is kratom a major issue or concern in your personal work experience?

Answered: 102   Skipped: 3



Q4: Is kratom a major issue or concern in your personal work experience?

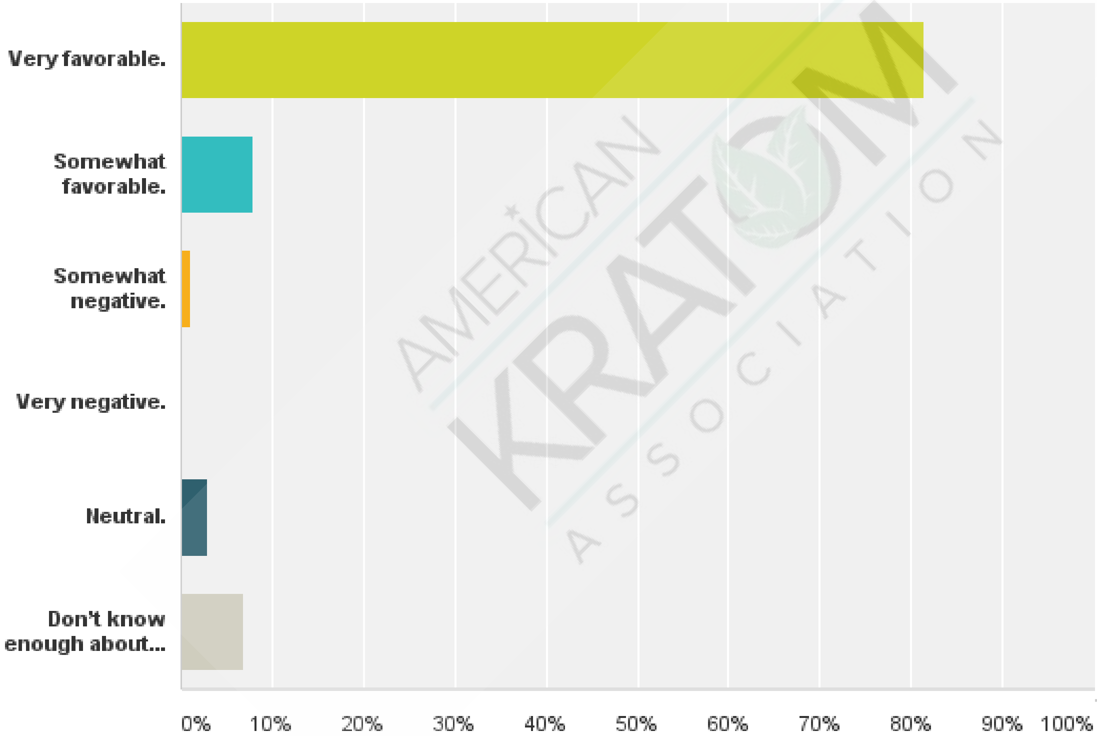
Answered: 102   Skipped: 3



Answer Choices	Responses	
Yes.	4.90%	5
No.	92.16%	94
Don't know/not sure.	2.94%	3
Total		**102**

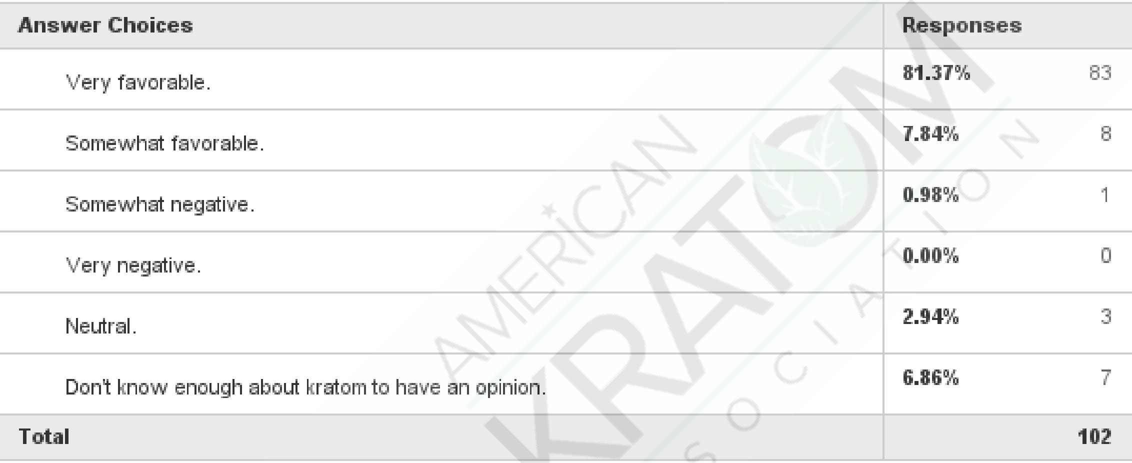
Q5: Do you have a favorable or unfavorable opinion of kratom?

Answered: 102 Skipped: 3



Q5: Do you have a favorable or unfavorable opinion of kratom?

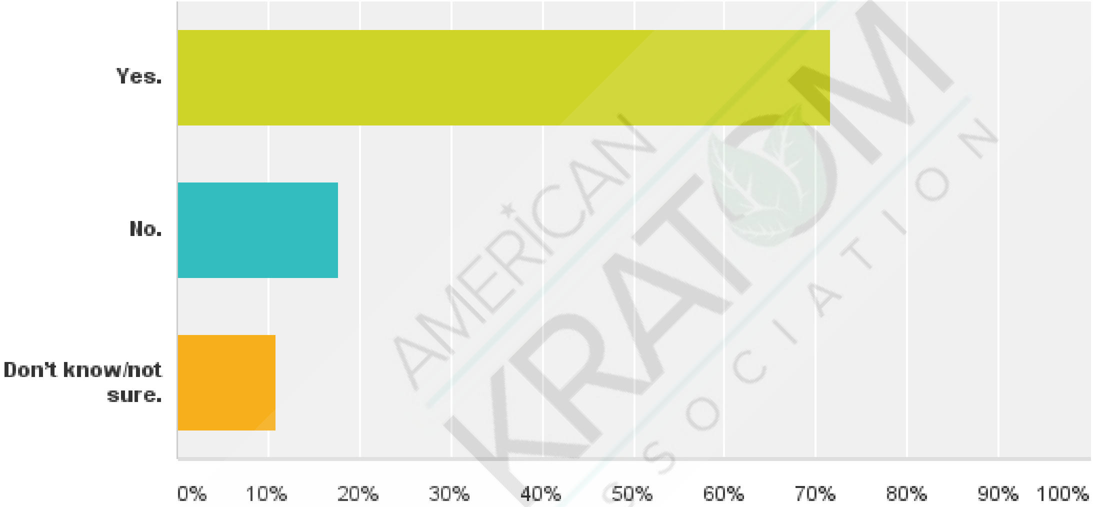
Answered: 102   Skipped: 3



Answer Choices	Responses	
Very favorable.	**81.37%**	83
Somewhat favorable.	**7.84%**	8
Somewhat negative.	**0.98%**	1
Very negative.	**0.00%**	0
Neutral.	**2.94%**	3
Don't know enough about kratom to have an opinion.	**6.86%**	7
Total		**102**

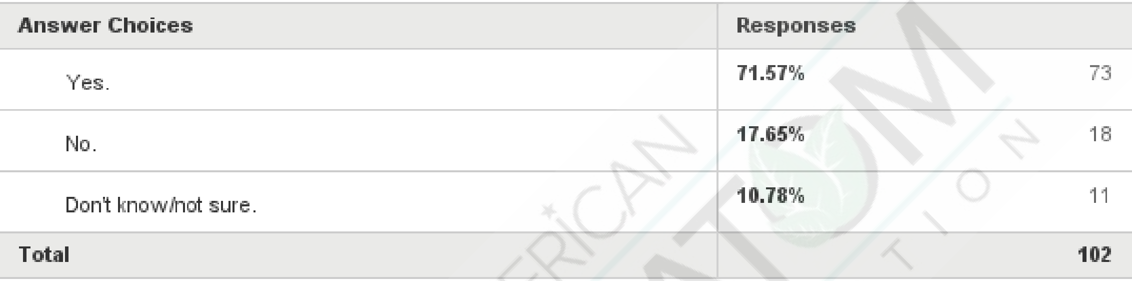
Q6: Have you ever dealt with any patient or other individual who is a kratom consumer?

Answered: 102   Skipped: 3



Q6: Have you ever dealt with any patient or other individual who is a kratom consumer?

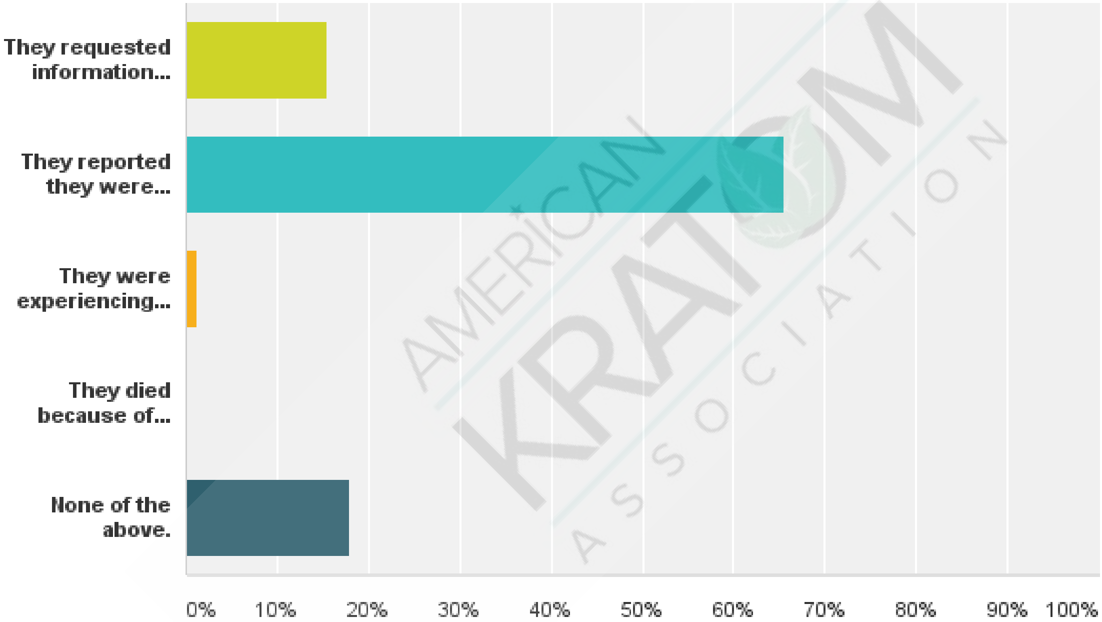
Answered: 102   Skipped: 3



Answer Choices	Responses	
Yes.	**71.57%**	73
No.	**17.65%**	18
Don't know/not sure.	**10.78%**	11
Total		**102**

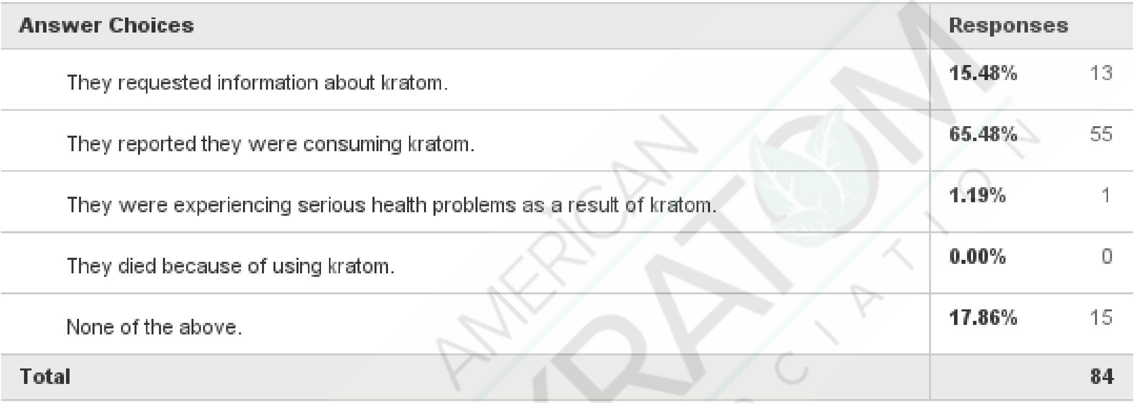
Q7: A follow-up question: What was the nature of the experience you had with a kratom consumer? (Pick the one most reflective of your personal experience.)

Answered: 84   Skipped: 21



Q7: A follow-up question: What was the nature of the experience you had with a kratom consumer? (Pick the one most reflective of your personal experience.)

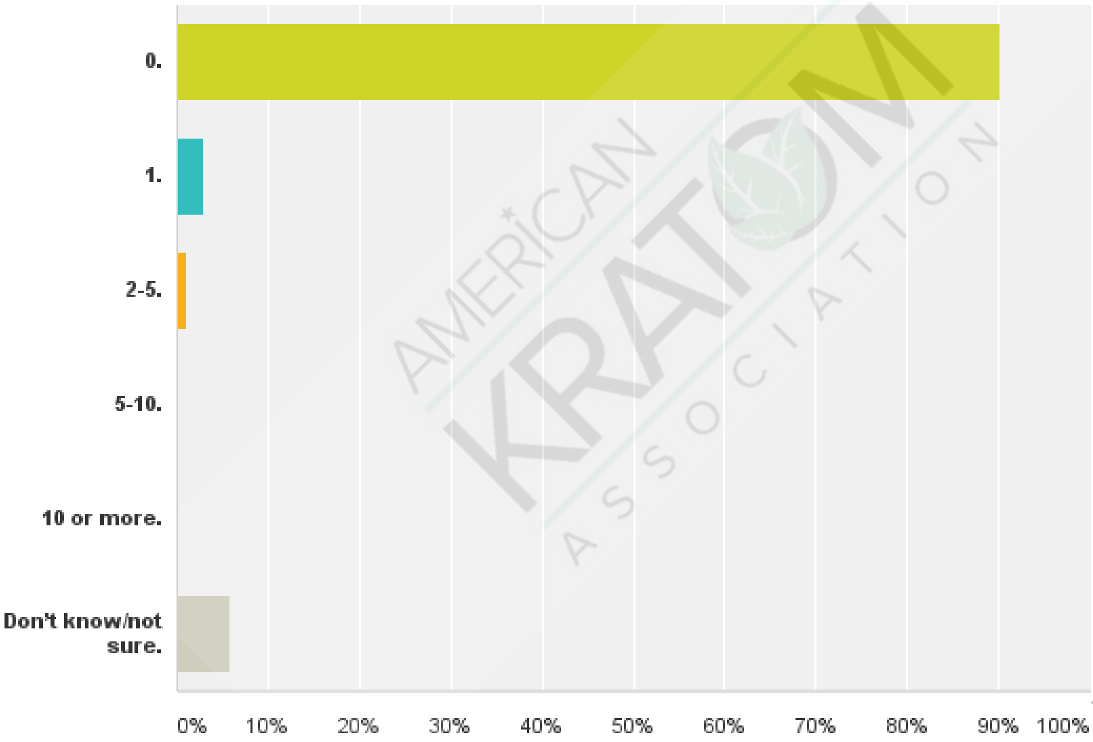
Answered: 84 Skipped: 21



Answer Choices	Responses	
They requested information about kratom.	15.48%	13
They reported they were consuming kratom.	65.48%	55
They were experiencing serious health problems as a result of kratom.	1.19%	1
They died because of using kratom.	0.00%	0
None of the above.	17.86%	15
Total		**84**

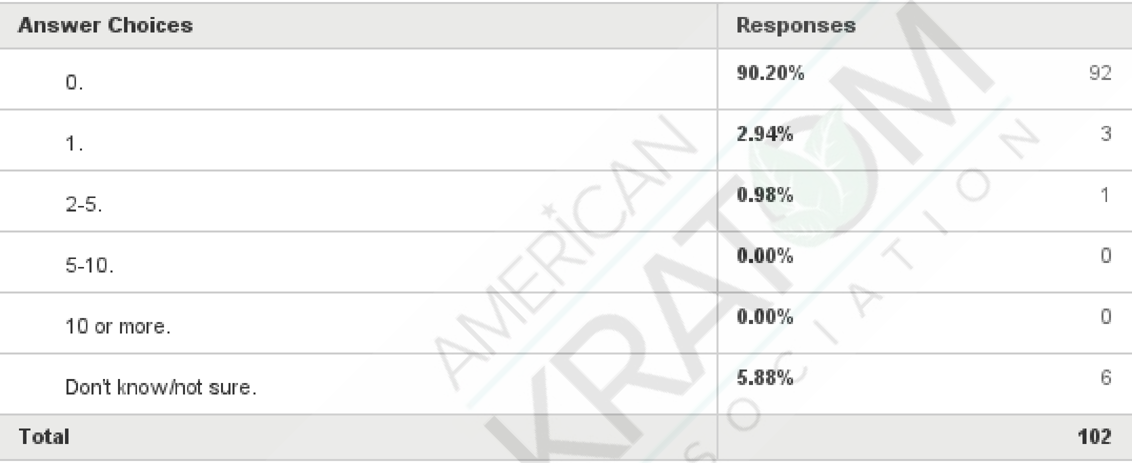
Q8: How many major problem cases (if any) directly attributable to kratom have you dealt with personally?

Answered: 102   Skipped: 3



Q8: How many major problem cases (if any) directly attributable to kratom have you dealt with personally?

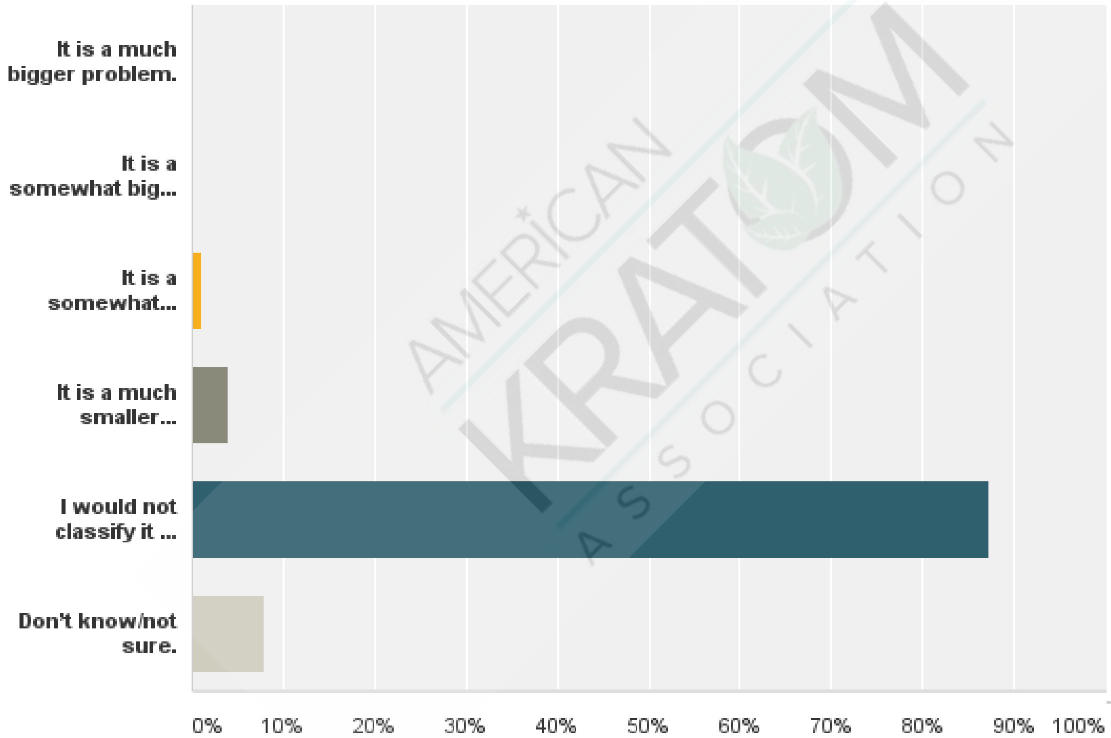
Answered: 102   Skipped: 3



Answer Choices	Responses	
0.	90.20%	92
1.	2.94%	3
2-5.	0.98%	1
5-10.	0.00%	0
10 or more.	0.00%	0
Don't know/not sure.	5.88%	6
Total		**102**

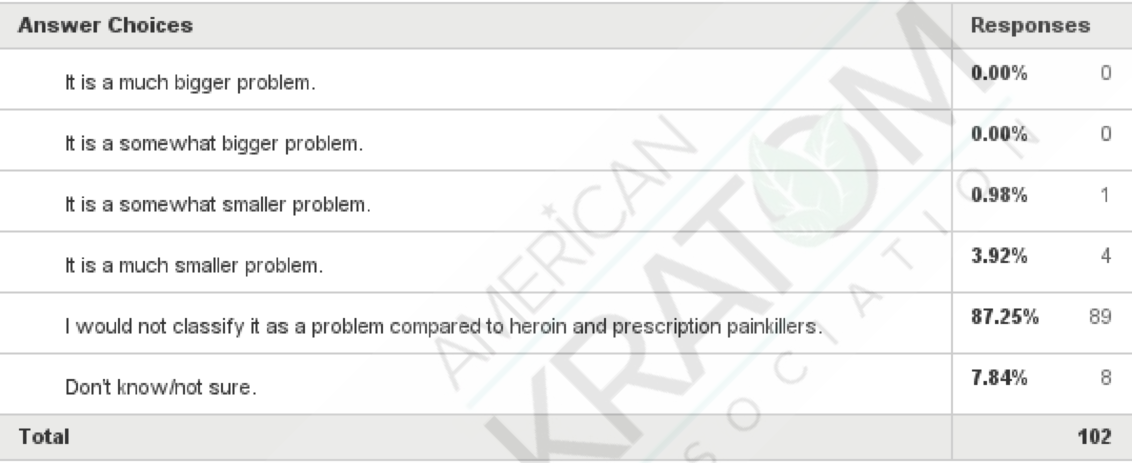
Q9: Based on your personal experience, how would you say the kratom issue stacks up in relation to heroin use and prescription painkiller abuse?

Answered: 102 Skipped: 3



Q9. Based on your personal experience, how would you say the kratom issue stacks up in relation to heroin use and prescription painkiller abuse?

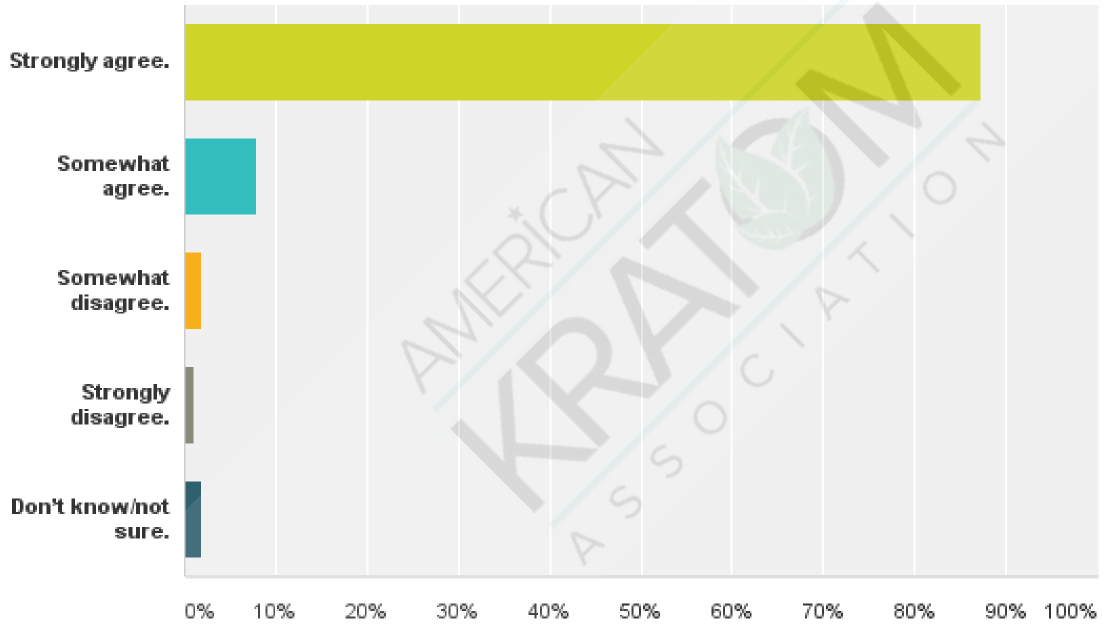
Answered: 102 Skipped: 3



Answer Choices	Responses	
It is a much bigger problem.	**0.00%**	0
It is a somewhat bigger problem.	**0.00%**	0
It is a somewhat smaller problem.	**0.98%**	1
It is a much smaller problem.	**3.92%**	4
I would not classify it as a problem compared to heroin and prescription painkillers.	**87.25%**	89
Don't know/not sure.	**7.84%**	8
Total		**102**

Enforcement Agency – the DEA – should focus its efforts on halting the heroin and prescription painkiller opioid crisis in America and not be distracted by lesser issues.”

Answered: 102 Skipped: 3



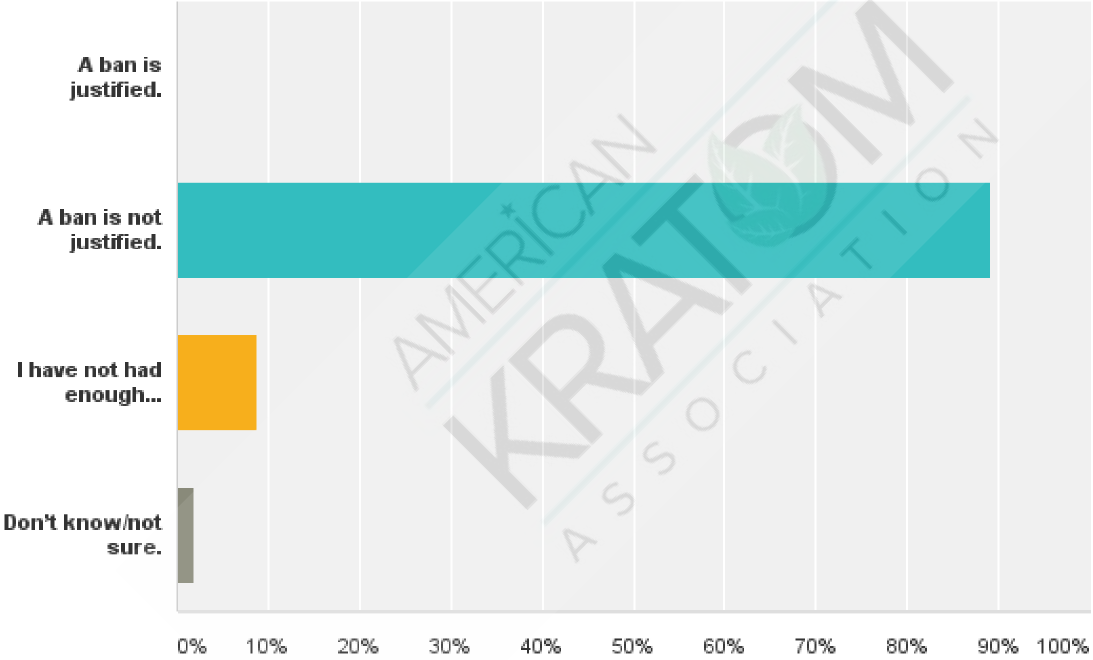
Enforcement Agency – the DEA – should focus its efforts on halting the heroin and prescription painkiller opioid crisis in America and not be distracted by lesser issues.”

Answered: 102   Skipped: 3

Answer Choices	Responses	
Strongly agree.	**87.25%**	89
Somewhat agree.	**7.84%**	8
Somewhat disagree.	**1.96%**	2
Strongly disagree.	**0.98%**	1
Don't know/not sure.	**1.96%**	2
Total		**102**

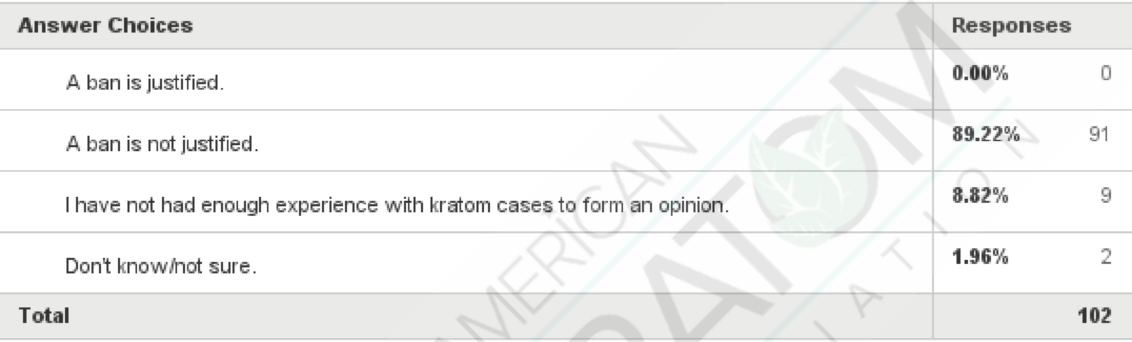
Q11: Do you think a ban on the herb kratom is justified based on your professional experience?

Answered: 102   Skipped: 3



Q11: Do you think a ban on the herb kratom is justified based on your professional experience?

Answered: 102 Skipped: 3



Answer Choices	Responses	
A ban is justified.	0.00%	0
A ban is not justified.	89.22%	91
I have not had enough experience with kratom cases to form an opinion.	8.82%	9
Don't know/not sure.	1.96%	2
Total		**102**

Florida Drug and Law Enforcement Official Statewide Intelligence Drug Report

February 9, 2016

A review of available law enforcement and laboratory sources in Florida demonstrates that Kratom does not currently constitute a significant risk to the safety and welfare of Florida residents. According to the Florida Department of Health (DOH), no pervasive health issues have been attributed to the ingestion of Kratom products in Florida. Diagnostic tests that would reveal the presence of Mitragynine are not routinely performed on patients during emergency room visits. Therefore, arriving at the precise number of Mitragynine exposures that result in harm to the patient is difficult to assess.

Kratom and the Impact to Florida

Product #15-141 UNCLASSIFIED//FOR OFFICIAL USE ONLY
Kratom – Mitragyna speciosa The Impact to Florida
Florida Department of Law Enforcement Rick Swearingen, Commissioner
December 2015
Kratom – Mitragyna speciosa December 2015

Executive Summary

+ Kratom (Mitragyna speciosa) is a plant substance which is marketed and commercially available over the Internet and in Florida at many convenience stores, gas stations, head shops, and vapor stores. The ingestion of Kratom involves the use of the leaves either whole or crushed, prepared as a tea, smoked or chewed; or as an extract or encapsulated powder.

Mitragynine and 7-Hydroxymitragynine are the major active alkaloids found in the Kratom plant; neither Mitragynine nor 7-Hydroxymitragynine are enumerated as controlled substances under federal statute 21 USC 844 (Controlled Substance Act) or Florida Statute 893 (Drug Abuse Prevention and Control). Accordingly, all parts of the plant and its extracts are legal to cultivate, buy, possess, and distribute without a license or prescription. The U.S. Food and Drug Administration (FDA) has not approved Kratom for human consumption citing “inadequate information to provide reasonable assurance that such ingredients do not present a significant or unreasonable risk of illness or injury.” As a consequence, the FDA issued an Import Alert regarding shipments of dietary supplements and bulk dietary ingredients that are, or contain Mitragyna speciosa or Kratom allowing for the detention without physical examination of specified products from the firms listed in Import Alert 54-15. This alert is updated as new firms are added to the list.

Kratom has been described as producing both stimulant and sedative effects depending on dosage. Reportedly, Kratom use at low doses produces stimulant effects and at high doses sedative effects. Side effects on the body include nausea, itching, sweating, dry mouth, constipation, increased urination and loss of appetite. Some literature suggests that Kratom/Mitragynine may have a role in treating the withdrawal symptoms of opiate addiction. Academic studies are ongoing. Drug Enforcement Administration (DEA) literature indicates no legitimate medical use for Kratom in the United States.

The FDLE Laboratory System reflected a low number of submissions (1 to 6) annually between 2011 and 2015. Seven labs associated with various counties also reflected a low number of submissions (1 to 2) over multiple years. The laboratory utilized in toxicology testing by Florida Medical Examiners districts reported that from January 1 through November 2015, Mitragynine was present in ten cases analyzed by the lab. Some Florida counties have proposed ordinances related to Kratom; however at this time, Sarasota County is the only county known to have passed an ordinance related to the marketing of “designer drugs” among which is Kratom. This ordinance puts the responsibility on the seller of the substances. The Florida Legislature considered a proposed bill to schedule Kratom during the 2015 legislative session, though it died in committee. A similar bill filed in anticipation of the 2016 legislative session proposes to add Mitragynine and 7-Hydroxymitragynine to Schedule I of Controlled Substances found in Florida Statute Section 893.03.

Several states responded to a request for information regarding Kratom. Among the states that responded, three (3) have regulated or scheduled Mitragynine and 7-Hydroxy-mitragynine as controlled substances with two (2) others considering legislation in reference to Kratom. Illinois and Louisiana enacted legislation with respect to the use of or distribution to Kratom to minors.

A review of information currently available through identified law enforcement and laboratory sources in Florida indicates that Kratom does not constitute a significant risk to the safety and welfare of Florida residents. The Florida Department of Health (DOH) reports no pervasive health issues attributed to the ingestion of Kratom products in Florida, though diagnostic tests that would reveal the presence of Mitragynine are not routinely performed on patients during emergency room visits. It is unclear how many Mitragynine exposures resulted in harm. Kratom use or abuse is not monitored by any national drug abuse surveys and much of the information regarding possible deleterious effects of Kratom use or abuse remains anecdotal.

This drug report will examine the extent to which "Kratom", or more specifically Mitragyna speciosa, and the botanical mixtures derived from it are impacting public safety in the state of Florida.

BACKGROUND:

Mitragynine and 7-Hydroxymitragynine are the major active alkaloids found in the Kratom plant (Mitragyna speciosa), a tropical tree related to the coffee plant which is indigenous to Thailand, Malaysia, and Myanmar in Southeast Asia.

The ingestion of Kratom involves the use of the leaves, which are approximately five inches wide and seven inches long, and are either whole or crushed, prepared as a tea, smoked or chewed; it can also be found in the form of an extract, or encapsulated powder. Neither Mitragynine nor 7-Hydroxymitragynine is currently enumerated as a controlled substance under federal statue 21 USC 844 (Controlled Substances Act); or within Florida under Florida Statute 893 (Drug Abuse Prevention and Control). This means that all parts of the plant and its extracts are legal to cultivate, buy, possess, and distribute without a license or prescription. The substance is available on the Internet and in some instances is marketed as a legal psychoactive product with alleged medicinal benefits. Some literature suggests that Kratom/Mitragynine may have a role in treating the withdrawal symptoms of opiate addiction. Academic studies including research by the University Of Mississippi School Of Pharmacy are ongoing.

In 2015, the U. S. Food and Drug Administration (FDA) issued an Import Alert regarding shipments of dietary supplements and bulk dietary ingredients that are, or contain, Mitragyna speciosa or Kratom. Import Alert 54-15 issued by the FDA states that U.S. Customs and Border Protection (CBP) districts may detain, without physical examination, the specified products from the firms identified in the alert. The specified dietary supplements and bulk dietary ingredients from the firms listed on the Import Alert have been found to contain Kratom.1

The FDA stated in their alert that "there does not appear to be a history of use or other evidence of safety establishing that Kratom will reasonably be expected to be safe as a dietary ingredient." Due to "inadequate information to provide reasonable assurance that such ingredients do not present a significant or unreasonable risk of illness or injury," the FDA has not approved Kratom for human consumption. At the request of the FDA, Customs and Border Protection (CBP) at the Port of Cincinnati, Ohio has seized seventy one shipments with an aggregate total of five-thousand four-hundred pounds of Kratom powder.

Kratom is not the first popular dietary substance to be the subject of an FDA alert. In November 2003 the FDA issued alert P04-106 to remove ephedra-containing dietary supplements from the market. The FDA alert on the ingestion of ephedra-based dietary supplements was not without controversy, and the ban on ephedra and ephedra-containing alkaloids was briefly overturned because of pressure applied by members of the supplement industry before ultimately being upheld. Like Kratom, ephedra is also a botanical derivative that has traditionally been used for a variety of medicinal purposes, including weight loss and to provide an increase in stamina. The FDA acted in response to the growing concern about the possible increased risk of ephedra users suffering heart attacks and strokes. These concerns were exacerbated by the well-publicized deaths of four (4) high-profile professional athletes who were known to be ingesting ephedrine-based dietary supplements and those supplements were found partially responsible for their deaths.

In Thailand, where the Kratom plant is indigenous, the plant has traditionally been ingested by laborers as a stimulant. In 1943, the Thai government passed a law making it illegal to plant Kratom trees and ordered all Kratom plants destroyed because opium users were substituting the Kratom leaves for opium, causing the Thai government to lose tax revenue derived from the opium trade. Opium users found Kratom use caused milder side effects than opium, and by using Kratom leaves the users were able to wean themselves from opium addiction. Thailand's efforts to eradicate Kratom were ineffective because the tree flourished naturally. In 1979, the Thai government scheduled Kratom as a narcotic in an effort to control its sale and consumption.2 The Thai Office of Narcotics Control Board is considering decriminalizing Kratom in Thailand because of the plant's historical and cultural significance to the Thai people. The possibility exists that the Board is considering lifting the ban on Kratom to take advantage of the potentially large North American market.

According to the DEA Kratom Fact Sheet issued in January 2013, there is no legitimate medical use for Kratom in the United States. The DEA Fact Sheet on Kratom also states that Kratom abuse is not monitored by any national drug abuse surveys, limiting available information on user populations.3

Kratom has been described as producing both stimulant and sedative effects. According to DEA, "at low doses Kratom produces stimulant effects with users reporting increased alertness, physical energy, and talkativeness. At high doses, users experience sedative effects. Kratom' s side effects on the body include nausea, itching, sweating, dry mouth, constipation, increased urination and loss of appetite. Kratom consumption can lead to addiction."4

Information on the use of Kratom in the U.S. is anecdotal. In a notable Swedish study the primary chemical component found in Kratom (Mitragynine) was one of the components found to be present in nine (9) incidents of fatal intoxication involving a product sold on the Internet called "Krypton". According to the Swedish study, "Krypton" consisted of powdered Kratom leaves together with a more potent substance (O-Desmethyltramadol).5 In the U.S., two (2) deaths in 2013 reference Kratom as a factor. A Colorado man died from what was reportedly apparent acute Mitragynine toxicity; and in Washington, a woman who had reportedly ingested Kratom also died, but in that case, no determination could be made that Kratom was a key factor that led to the death because another potent substance was also present in the toxicology. In Florida, a twenty-four-year-old United States Airman died in Santa Rosa County in August 2013; according to the Medical Examiner's (ME) report, the cause of death was "Acute Mitragynine Intoxication" and the manner of death was "Accident."

THE FLORIDA PERSPECTIVE:

In 2014, the family of a subject whose manner of death was deemed a suicide in Palm Beach County attributed the death to an addiction to Kratom. In that case, Mitragynine quantification was not available rendering a determination as to the possible effect of Kratom on the subject unavailable as well. The presence of other controlled substances may have contributed to the subject's state of mind at the time of the suicide. This incident was causal in the Broward County Commission's proposal to ban the distribution of Kratom in the county in 2014. The Broward Commission ultimately decided to await further research before proposing a ban on the distribution of Kratom in Broward County.

In an effort to ascertain how widely available Kratom was in the region and to determine if Kratom and similar drugs posed a significant threat to public safety in the area, FDLE special agents in Pensacola located over forty locations including gas stations, "head shops", Vapor stores, and carry-outs selling derivatives of Kratom and made purchases of these products. These purchases usually consisted of bottles of commercially available "Viva Zen" or "Fly Away", which are liquid forms of Kratom, or commercially prepared packages of Kratom capsules or tablets. Agents also purchased Kratom in the form of a plastic cigarette which the agents had previously only seen online. This was the only occasion the agents found a plastic cigarette for sale in a store. On two occasions, agents went to a specific "head shop" in an undercover capacity and observed a clear plastic bag in a display case containing what the proprietor claimed was Kratom. The proprietor told the agents, who were posing as customers, that he had packaged the Kratom for sale in the store, and that the Kratom he had personally packaged was cheaper than the commercially available packages of “American Kratom” he also sold. Agents purchased both the commercially packaged “American Kratom” and the Kratom packaged by the proprietor from this location. Agents were also able to purchase Kratom online utilizing Craigslist on one occasion. A check conducted at a regional medical center for Kratom-related health issues in the Pensacola area was negative. None of the six other FDLE regions report any significant information in reference to Kratom.

In Florida, Sarasota County successfully enacted an ordinance in reference to Kratom focused on the marketing, packaging and sale of so called “designer drugs”. The ordinance regulates retail establishments in an effort to attack the abuse of synthetic drugs rather than focusing on the chemical components of designer drugs which can be modified molecularly nearly as fast as the chemical components are scheduled. Kratom was included in the Sarasota County ordinance though Kratom itself is not a synthetic. Sarasota County Ordinance 2014-013 defines Kratom as “an herbal psychotropic stimulant and opioid substitute with no legitimate medical use” and bans the manufacture, display, sale, possession, and transport of Kratom.[6]

FDLE Lab Submissions Mitragynine

2011	1
2012	0
2013	4
2014	3
2015	6

Florida Law Enforcement Laboratories

Palm Beach County	2
Pinellas County	2
Indian River County	2
Manatee	0
Sarasota County	0
Broward	1
Miami-Dade	1

To date, FDLE laboratory submissions from 2011 to 2015 have been low; one (1) in 2011; none in 2012; four (4) in 2013; three (3) in 2014; and six (6) through November 2015.

Labs across Florida handling submissions outside of FDLE were queried in reference to submissions of Kratom, or the primary active alkaloid in the plant, Mitragynine. Palm Beach County reported that since 2008, they have had two (2) submissions, both of them containing Mitragynine alone. The Pinellas County lab also reported two (2) submissions that mass spectrometer analysis determined to be Mitragynine and Hydroxymitragynine. Indian River County Laboratory reported two (2) lab submissions, both in 2013, relative to Kratom; one (1) was a package of “Spice”, and the other was a powder/plant mixture. In both of the Indian River cases, the lab reported, “the presence of Mitragynine was indicated but not confirmed”. Manatee County reported no submissions of Kratom or Mitragynine. The lab in Sarasota

County reported no laboratory submissions in reference to Kratom or Mitragynine. Broward County reported one (1) submission of Mitragynine in 2012. The laboratory in Miami-Dade had one submission of Mitragynine in 2012.

A survey of the designated Florida High Intensity Drug Trafficking Areas (HIDTA) revealed no significant report of Kratom activity in any of the HIDTA jurisdictions. The Florida HIDTA regions are divided as follows: The North Florida HIDTA region consists of 10 counties with a population of 1,843,371. The Central Florida HIDTA consists of eight (8) counties with a population of 5,711,068. The South Florida HIDTA consists of four (4) counties with a population of 5,730,701. The three (3) Florida HIDTA's have a combined total population of 13,285,140 (approximately 67%) of Florida's 19,893,297 residents. The number of Florida residents residing outside of a HIDTA region is 6,608,157. The graphic below depicts the three Florida HIDTA areas of responsibility: Wuesthoff Reference Laboratories of Melbourne Florida, which conducts toxicology testing for seven of Florida's Medical Examiner districts, reported that from January 1 through November 2015, Mitragynine was present in eleven cases analyzed by the lab. These results did not indicate that Mitragynine was the cause of death, but rather that the substance was present at the time of the analysis.

Florida's twenty-four Medical Examiner's (ME) districts were also surveyed in reference to incidents of Mitragynine and 7-hydroxymitragynine. Nineteen ME districts responded and reported a total of eight (8) incidents involving a positive result for the presence of Kratom. Two (2) of the incidents listed the cause of death as gunshot wounds; one (1) of those was a suicide and numerous drugs, including cyclobenzaprine, cocaine metabolite, diphenhydramine were also present, and the other involved the intrauterine death of a fetus that died as the result of the mother sustaining a non-fatal (to the mother) gunshot wound to the stomach.

District 1 reported one (1) death from multiple drug intoxication where Kratom was present. The cause of death listed Alprazolam, Gabapentin, and Clonazepam, with multiple other drugs present.

District 9 (Orlando) reported three (3) deaths where Kratom was present but not the cause of death. One (1) of these deaths was found to be natural due to heart disease, though Mitragynine, caffeine, caffeine metabolite, and alprazolam were also present. Both of the other District 9 deaths were determined to be accidental; one (1) involved acute heroin and cocaine toxicity and the other involved intoxication by acetyl fentanyl.

District 17 (Ft. Lauderdale) reported one (1) incident, and the cause of death was high levels of fentanyl and cyclobenzaprine with Kratom listed as contributory but not quantifiable.

District 19 reported one (1) incident of combined drug toxicity in which the primary toxicity was due to Kratom usage. The Medical Examiner did not provide a quantitative analysis of the Kratom or any of the other drugs that may have been present at the time of death.

A few states have banned or restricted the sale, possession, and/or use of Kratom. In February 2015, the Office of Statewide Intelligence (OSI) requested information from other states in reference to Kratom; responses varied. For instance, the Northern California HIDTA reported increased popularity and availability of Kratom, which is not regulated in California. At the request of the Food and Drug Administration (FDA), U. S. Marshals in California seized twenty-five thousand pounds of Kratom with an estimated value of five million dollars. Melinda Plaiser, an FDA official, stated “We have identified Kratom as a botanical substance that poses a risk to public health and has the potential for abuse.” The wholesaler from whom the Kratom was seized had promoted the product on its website for “use in the diagnoses, cure, mitigation, treatment or prevention of disease”, but the FDA maintains that Kratom is not for human consumption. In response, the FDA filed a complaint in the US District Court for the Central District of California alleging that Kratom was not an approved drug under the Federal Food, Drug, and Cosmetic Act.7

In Vermont, the Board of Health declared Mitragynine and 7-hydroxymitragynine alkaloids of interest during an initiative to update regulations on bath salts and other synthetic cathinones. Vermont’s criteria for adding a substance to the regulated drugs list are case reports of the substance within Vermont or literature reviews of adverse effects of the substance. Medical examiners in Vermont have not attributed any deaths due to Mitragynine toxicity. In lieu of the DEA drug scheduling system, Vermont implemented drug “regulations” to monitor substances.

The Kentucky Office of the Governor reported that though Kratom is not currently legislated in the state, a ban is under consideration. During the previous year, Kentucky officials noted only two (2) reported incidents relative to Kratom possession, and one of those was considered noteworthy only because the Kentucky resident was in possession of two (2) gallon-size baggies of Kratom purchased as a homeopathic remedy. The Kentucky Office of the Governor also expressed the opinion that Kratom will eventually be banned in the state because of bans already enacted on salvia and synthetic marijuana. Kentucky looks “unfavorably” on any product that produces similar physical effects as already banned substances. The Kentucky Office of the Governor postulated that the possession of Kratom would likely become a Class B misdemeanor with a penalty of incarceration not to exceed thirty days.

The Michigan Poison Control database reports only two (2) hospital visits in the state in reference to Kratom which is currently legal in the state. A house bill was proposed in 2014 which would have made Kratom a schedule V drug, but no legislation has been enacted in Michigan to date.

In Indiana, Kratom has been illegal since 2012 because it contains Mitragynine and 7-Hydroxymitragynine, both banned substances. The Indiana Poison Control Center reported just one (1) case of Kratom exposure in 2012, two (2) cases in 2013, and three (3) cases in 2014. Indiana experiences too few incidents in reference to Kratom to consider it a significant problem.

The Chief Deputy for the Ohio Attorney General reported that it is not illegal to possess Kratom in Ohio, though in Ohio it is illegal to possess something that is intended to be used as a drug unless it is approved as a drug by the FDA.

In North Carolina, Kratom possession is legal, but when encountered officials typically see Kratom in submissions along with scheduled synthetic cannabinoids.

After state laboratories documented four (4) cases of Kratom possession, in 2013, Wisconsin enacted legislation making the possession, distribution, and manufacture of Kratom illegal. In Wisconsin, the controlled substances board can consider the findings of the FDA and the DEA when considering passing state legislation in reference to any substance that has been found to have the potential for abuse, and has made Kratom a Schedule I substance. No known deaths have been attributed to Mitragynine toxicity in Wisconsin, and the legislature is considering removing Kratom from the Schedule I classification.

In Tennessee it has been illegal to sell or to possess Mitragynine or hydroxymitragynine since July 2013. The Tennessee Bureau of Investigation (TBI) reported that though Kratom had been seen in laboratory submissions around the state, no Tennessee Medical Examiner information is available. Kratom is not currently a scheduled substance in Tennessee; however, possession of Kratom has been categorized as a Class A misdemeanor which has deterred merchants from selling Kratom-based products.

In North Dakota, there exists no legislation in reference to Kratom, and recorded no instances of Kratom use in the state.

Illinois does not record instances of Kratom usage or abuse. However, the state has enacted legislation making ingestion of Kratom illegal for persons under eighteen years old. Kratom is legal for persons over eighteen years of age in Illinois.

Louisiana passed Act Number 355 in 2012 prohibiting the distribution of products containing Mitragyna speciosa to minors. The penalty for violating this legislation in Louisiana is a maximum five hundred dollar fine and not more than six months imprisonment. In mid-September 2015, a West Baton Rouge Parrish, Louisiana Sheriff's Deputy performed a car stop for a traffic violation on a vehicle travelling eastbound on Interstate 10. A probable cause search of the vehicle was conducted and eighteen pounds of powdered Kratom and several hundred canisters of butane were found in the passenger compartment. The Deputy did not seize the butane or the Kratom because Kratom is not a controlled substance in Louisiana. The driver, a resident of South Carolina, was allowed to leave with his vehicle. The relation between the Kratom powder and the butane is unknown, although some open source materials report that butane is sometimes used during Kratom extraction processes.

CONCLUSION:

A review of available law enforcement and laboratory sources in Florida demonstrates that Kratom does not currently constitute a significant risk to the safety and welfare of Florida residents. According to the Florida Department of Health (DOH), no pervasive health issues have been attributed to the ingestion of Kratom products in Florida. Diagnostic tests that would reveal the presence of Mitragynine are not routinely performed on patients during emergency room visits. Therefore, arriving at the precise number of Mitragynine exposures that result in harm to the patient is difficult to assess.

The lack of Mitragynine ingestion and exposure reporting continues to be an intelligence gap. Legislative attempts to regulate Kratom in Florida in 2015, specifically HB287 and SB764, both of which would have made Kratom a Schedule I controlled substance, failed to be passed into law. The Florida legislature will soon consider HB0073 which would, if enacted, place Mitragynine and 7-Hydroxymitragynine, the major active alkaloids of the Kratom plant, on the list of Controlled Substances under Schedule I listed in Florida Statute 893.03. By definition, a Schedule I drug is defined by the Drug Enforcement Agency (DEA) as "substances, or chemicals with no currently accepted medical use and a high potential for abuse. Schedule I drugs are the most dangerous drugs of all the drug schedules with potentially severe psychological or physical dependence." Heroin, LSD, and marijuana are all Schedule I drugs. By comparison, "Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, less abuse potential than Schedule I drugs, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous." Cocaine, methamphetamine, and fentanyl are three examples of Schedule II drugs. Drugs with lower potential for dependence fall in to Schedule III, and include substances such as Tylenol with codeine, anabolic steroids, and testosterone. The categories Schedule IV and Schedule V each have lower potential for abuse and risk of dependence respectively.

A host of media articles and a review of open-source website reporting in Florida reveal that there are Floridians that ingest Kratom or its derivatives on a regular basis and see the use of Kratom as a homeopathic or alternative therapy for such maladies as depression, Lyme disease, chronic pain, and drug addiction. These Kratom consumers continue to extol the plant for its therapeutic properties and decry the Florida legislature's attempt to ban, or regulate, Kratom. There is currently no accepted or recognized medical use for Kratom. Kratom use is not monitored by any national drug abuse surveys and much of the information regarding any deleterious effects of Kratom use or abuse remains anecdotal and is another identified intelligence gap.

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Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb *Mitragyna speciosa*

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Abstract

Mitragynine is an indole alkaloid isolated from the Thai medicinal plant *Mitragyna speciosa*. We previously reported the morphine-like action of mitragynine and its related compounds in the in vitro assays. In the present study, we investigated the opioid effects of 7-hydroxymitragynine, which is isolated as its novel constituent, on contraction of isolated ileum, binding of the specific ligands to opioid receptors and nociceptive stimuli in mice. In guinea-pig ileum, 7-hydroxymitragynine inhibited electrically induced contraction through the opioid receptors. Receptor-binding assays revealed that 7-hydroxymitragynine has a higher affinity for μ-opioid receptors relative to the other opioid receptors. Administration of 7-hydroxymitragynine (2.5–10 mg/kg, s.c.) induced dose-dependent antinociceptive effects in tail-flick and hot-plate tests in mice. Its effect was more potent than that of morphine in both tests. When orally administered, 7-hydroxymitragynine (5–10 mg/kg) showed potent antinociceptive activities in tail-flick and hot-plate tests. In contrast, only weak antinociception was observed in the case of oral administration of morphine at a dose of 20 mg/kg. It was found that 7-hydroxymitragynine is a novel opioid agonist that is structurally different from the other opioid agonists, and has potent analgesic activity when orally administered.
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Keywords: Mitragynine; 7-Hydroxymitragynine; Morphine; Opioid receptor; Analgesic; Ileum

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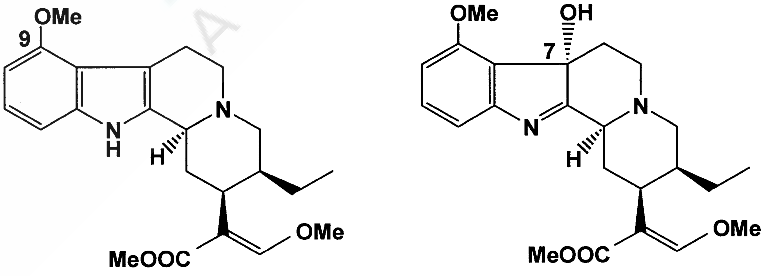
Introduction

The leaf of *Mitragyna speciosa* (*kratom* in Thai) has been used in Thailand for its opium-like effect (Burkill, 1935) and its coca-like stimulant ability to combat fatigue and enhance tolerance to for hard work under a scoring sun (Grewal, 1932; Suwanlert, 1975). Additionally, it has been used to treat diarrhea and to wean addicts off morphine (Suwanlert, 1975; Jansen and Prast, 1988).

We have studied the pharmacological activities of an indole alkaloid isolated from Uncaria hook (*Uncaria rhynchophylla*) that is used clinically for hypertension (Yano et al., 1991; Horie et al., 1992). Mitragynine (Fig. 1), the main component of the leaves of *Mitragyna speciosa*, is an indole alkaloid and structurally similar to Uncaria alkaloid. Mitragynine was reported to be comparable to codeine as an analgesic in dog, but it was not considered to act on opioid receptors (Macko et al., 1972; Jansen and Prast, 1988). We studied the effect of mitragynine on guinea-pig ileum contraction and found that mitragynine is an opioid receptor agonist (Watanabe et al., 1992, 1997). Some pharmacological investigations of mitragynine have also revealed that it has an antinociceptive action through the supraspinal opioid receptors, and that its action is dominantly mediated by μ- and δ-receptor subtypes in in vivo and in vitro studies (Matsumoto et al., 1996a,b; Tohda et al., 1997; Thongpradichote et al., 1998).

Our previous study demonstrated a potent opioid agonistic property of mitragynine and its derivative compound mitragynine pseudoindoxyl in in vitro experiments (Yamamoto et al., 1999). In guinea-pig ileum, mitragynine and mitragynine pseudoindoxyl inhibit the vagally stimulated twitch contraction through opioid receptors. The effect of mitragynine pseudoindoxyl was 20-fold more potent than that of morphine. In mouse vas deferens, the effect of mitragynine pseudoindoxyl was 35-fold more potent than that of morphine. Mitragynine pseudoindoxyl was found to be a very potent μ- and δ-opioid agonist in both functional and binding assays (Yamamoto et al., 1999). In spite of its potent opioid effect, mitragynine pseudoindoxyl induced only a weak antinociceptive effect in the mouse tail-flick test in comparison with morphine (Takayama et al., 2002).

We previously compared the antinociceptive effect of *Mitragyna speciosa* and mitragynine in in vivo experiments, but the antinociceptive effect of mitragynine was less potent than that of the crude extract of *Mitragyna speciosa* (Watanabe et al., 1992, 1999). This finding means that minor constituents of *Mitragyna speciosa* may have a very potent antinociceptive effect. We surveyed the other constituents of *Mitragyna speciosa* and found a new compound 7-hydroxymitragynine (Fig. 1), as a minor constituent of this plant (Ponglux et al., 1994). 7-Hydroxymitragynine exhibited a higher



Mitragynine **7-Hydroxymitragynine**

Fig. 1. Chemical structures of mitragynine and 7-hydroxymitragynine.

potency than mitragynine in the guinea-pig ileum test and a high affinity for μ-opioid receptors in binding assays (Takayama et al., 2002).

In the present study, we examined the opioid effect of 7-hydroxymitragynine on isolated guinea-pig ileum contraction and receptor binding assays. In addition, we investigated the antinociceptive activity of subcutaneous and oral administration of 7-hydroxymitragynine in tail-flick and hot-plate tests, comparing its activity with morphine.

Methods

Animals

Male albino Dunkin-Hartley guinea-pigs (320–570 g) purchased from Takasugi Lab. Animals Co., Ltd. (Saitama, Japan) and male ddY mice (22–38 g) from Japan SLC Inc. (Shizuoka, Japan) were used. Animals were housed under conditions with controlled temperature (24 ± 2°C) and a 12-h light/dark cycle (lighting on at 0700), for at least 1 week before the start experiment. Food and water were available ad libitum. The experiments were performed in compliance with "Guiding Principles for the Care and Use of Laboratory Animals" approved by the Japanese Pharmacological Society and the guidelines approved by the Ethical Committee on Animal Care and Animal Experiment of Graduate School of Pharmaceutical Sciences, Chiba University. This study was carried out in accordance with the guidelines of the Ethics Committee of the International Association for the Study of Pain (Zimmermann, 1983).

Isolated tissue preparations

Male guinea-pigs were killed by stunning and exsanguination. Segments of the ileum were removed and placed in Krebs-Henseleit solution (mM): NaCl, 112.08; KCl, 5.90; $CaCl_2$, 1.97; $MgCl_2$, 1.18; NaH_2PO_4, 1.22; $NaHCO_3$, 25.00; and glucose, 11.49. The ileum was placed under 1 g tension in a 5 ml organ bath containing the nutrient solution. The bath was maintained at 37°C and continuously bubbled with a mixture of 95% O_2 and 5% CO_2. Tissues were stimulated by a platinum needle-ring (a ring was placed 20 mm above the base of a needle 5 mm in length) electrode. After 60 min equilibration in Krebs-Henseleit solution, the ileum was transmurally stimulated (Cox and Weinstock, 1966) with monophasic pulses (0.2 Hz and 0.1 ms duration) by a stimulator (SEN-7203, Nihon Kohden, Tokyo, Japan). Contractions were isotonically recorded by using a displacement transducer (NEC Type 45347, San-ei Instruments Ltd., Tokyo, Japan). Effects of drug treatments were examined on the twitch contractions evoked by transmural stimulation elicited through ring electrodes. At the start of each experiment a maximum response to acetylcholine (3 μM) was obtained in each tissue to check its stability. The mean amplitude of the electrically stimulated contraction was about 30% of the maximal response to acetylcholine (3 μM). The electrically-induced twitch contraction was almost abolished by tetrodotoxin (1 μM) and atropine (0.1 μM) as described previously (Watanabe et al., 1997). Thus the electrical stimulation induces cholinergic contraction in guinea-pig ileum (Brookes et al., 1991). All concentration-response curves were constructed in a cumulative manner. The height of the twitch response to transmural stimulation was measured before and after drug challenge. Contraction (%) is expressed as a percentage of twitch response to the transmural stimulation before the drug challenge.

Receptor binding assay

Male guinea-pigs were killed by stunning and cervical dislocation. The whole brain (excluding cerebellum) was quickly removed, weighed, placed in ice cold 50 mM Tris HCl buffer, pH 7.4, and frozen immediately. Frozen brains were stored at − 70°C until the assay. For each experiment, frozen brains from two animals were thawed and homogenized with a Polytron homogenizer (PT 10-35, Kinematica, Littau, Switzerland) for 60 sec in 50 mM Tris HCl (pH 7.4) and centrifuged at 49,000 g for 10 min (Childers et al., 1979). The pellet was re-homogenized and centrifuged again. For the binding assays, membrane fractions were suspended in assay buffer. Protein content was measured by using a DC-protein assay kit (Bio-Rad, Richmond, USA).

Saturation-binding isotherms were produced by incubating membrane proteins with radiolabeled compounds in different concentrations. Using the above solution, 0.1 ml aliquots of protein were added to 0.9 ml mixture solution of the labeled assay sample with unlabeled competing ligands in appropriate concentrations, which was solved in 50 mM Tris-HCl (pH 7.4) assay buffer. The assay solution contained one of the followings; 3 nM of [^{3}H][D-Ala^2, N-MePhe^4, Gly-ol^5]-enkephalin ([^{3}H]DAMGO), 3 nM of [^{3}H](5α,7α,8β)-(+)-*N*-(7-[1-pyrrolidinyl]-1-oxaspirol[4,5]dec-8-yl) benzeneacetamide ([^{3}H]U69593) or 1 nM of [^{3}H][D-Pen^2, D-Pen^5]-enkephalin ([^{3}H]DPDPE). The incubation periods were 3, 4, and 1 hr for [^{3}H]DAMGO, [^{3}H]DPDPE, and [^{3}H]U69593, respectively, at 25°C. The reaction was terminated by rapid filtration under reduced pressure through glass fiber filters (Whatman GF/B, presoaked in 0.3% polyethyleneimine) followed by the addition of 4 ml of ice-cold Tris-HCl buffer. Filters were further washed with 4 ml ice-cold buffer and left allowed to dry. Radioactivity bound to the filters was measured by liquid scintillation spectrometry (Aloka LSC-5100, Tokyo, Japan). Nonspecific binding for [^{3}H]DAMGO, [^{3}H]DPDPE or [^{3}H]U69593 was determined in the presence of 1 μM unlabeled DAMGO, naltrindole hydrochloride, and U69593, respectively. All values were presented as the mean ± s.e.mean. The apparent dissociation constant (K_D) and maximum binding site density (B_{max}) for radioligands were estimated by Scatchard analysis of the saturation. The ability of unlabeled drugs to inhibit specific radioligand binding was expressed as the IC_{50} value, which was the molar concentration of unlabeled drug necessary to displace 50% of the specific binding. Inhibition constants (Ki) of unlabeled compounds were calculated as described by Cheng and Prusoff (1973).

Tail-flick test

The method was adapted from that of D'Amour and Smith (1941). Mice responded to a focused heat stimulus by flicking or moving their tail from the path of the stimulus, thereby exposing a photocell located in the tail-flick analgesia meter (Ugo Basile Tail-flick Unit 7360, Ugo Basile, Comerio, Italy) immediately below the tail. The reaction time was automatically recorded. Prior to dosing, the nociceptive threshold was measured three times, and the mean of the reaction times was used as pre-drug latency for each mouse. The cut-off time of 10 sec was used to prevent tissue damage.

Hot-plate test

In the hot-plate test, an animal was placed in a glass cylinder of 24 cm diameter on a metal plate maintained at 55 ± 0.2°C, and the latency period until nociceptive responses such as licking, shaking of the limbs or jumping was measured. Prior to dosing, the nociceptive threshold was measured three times, and the mean of the reaction times was used as the pre-drug latency for each mouse. The cut-off time of 45 sec was used to prevent tissue damage.

Antinociception in tail-flick and hot-plate tests was quantified as the maximum possible effect (MPE) using the following formula:

$$\mathrm{MPE}\ (\%) = \frac{\text{Post} - \text{drug latency} - \text{Pre} - \text{drug latency}}{\text{Cut} - \text{off time} - \text{Predrug latency}} \times 100 \tag{1}$$

Drugs

The drugs used in this study were acetylcholine chloride (Dai-ichi Pharmaceutical Co., Tokyo, Japan), atropine sulfate (Nacalai tesque Inc., Tokyo, Japan), tetrodotoxine (Sankyo, Tokyo, Japan), morphine hydrochloride (Takeda Chemical Industries, Osaka, Japan), naloxone hydrochloride, DAMGO, U-69593, naltrindole hydrochloride (Sigma Chemical Co., St. Louis, USA) and [^{3}H]DAMGO, [^{3}H]DPDPE and [^{3}H]U69593 (NEN Life Science Products Inc., Boston, USA). Mitragynine was isolated from extract of leaves of *Mitragyna speciosa* and 7-hydroxymitragynine was synthesized as described previously (Ponglux et al., 1994; Takayama et al., 2002). The purity (>99%) of these compounds was checked by HPLC and ^{1}H-NMR (500 MHz) analysis (Takayama et al., 2002).

For bioassay and binding assay, mitragynine and 7-hydroxymitragynine were first dissolved in 100% dimethylsulfoxide to yield a 10 mM solution and then subsequently diluted with distilled water. Other drugs were dissolved in distilled water.

For antinociceptive tests, morphine and 7-hydroxymitragynine were first dissolved in 100% dimethylsulfoxide and then subsequently diluted with 0.5% carboxyl methylcellulose. The final concentration of dimethylsulfoxide was 4.8%. The vehicle did not affect the pain response in tail-flick and hot-plate tests (data not shown). All drug solutions were prepared just before the experiments. Solution was injected in a volume of 10 ml/kg body weight. Feeding probe was used when drugs and their vehicle were given p.o.

Statistical analysis

The data are expressed as the mean ± s.e.mean. Statistical analyses were performed with two-tailed Student's *t*-test for comparison of two groups, and by a one-way analysis of variance followed by a Bonferroni multiple comparison test for comparison of more than two groups. A P value < 0.05 was considered statistically significant.

Results

Effect of 7-hydroxymitragynine on electrically induced contraction in guinea-pig ileum

The inhibitory effect of 7-hydroxymitragynine on twitch contraction induced by electrical stimulation in guinea-pig ileum is shown in Fig. 2. The addition of 7-hydroxymitragynine inhibited

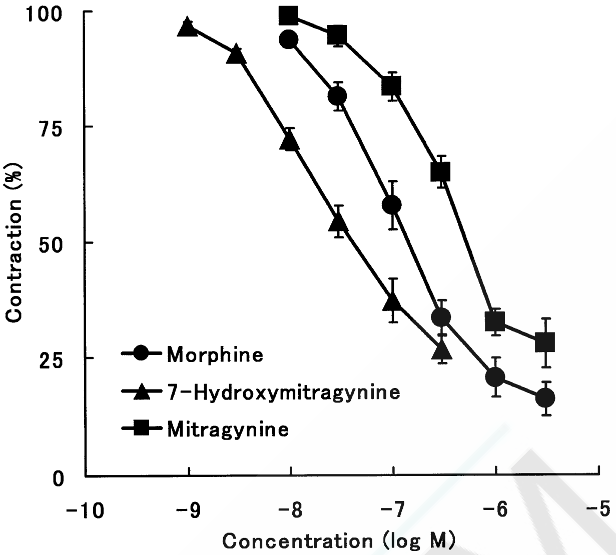


Fig. 2. Concentration response curves for inhibitory effects of 7-hydroxymitragynine and mitragynine on electrical stimulation-induced contraction in guinea-pig ileum. Each value is expressed as contraction percentage of the transmurally stimulated twitch contraction before the addition of samples. Data represent mean ± s.e.mean of five animals.

the electrically stimulated twitch contraction in a concentration-dependent manner as mitragynine and morphine did. The pD_2 values were 7.78 ± 0.08 for 7-hydroxymitragynine, 6.50 ± 0.06 for mitragynine and 7.02 ± 0.08 for morphine. Consequently, 7-hydroxymitragynine exhibits about 13- and 46-fold higher potency than morphine and mitragynine, respectively. Naloxone reversed the inhibitory effect of 7-hydroxymitragynine (control, 67.2 ± 5.3%, n = 5; naloxone 10 nM, 48.3 ± 10.2%, n = 5; naloxone 300 nM, − 8.0 ± 5.3%, n = 5, $P < 0.001$ vs. control) as well as that of morphine (control, 77.7 ± 7.8%, n = 5; naloxone 10 nM, 63.0 ± 9.8%, n=5; naloxone 300 nM, − 33.0 ± 13.5%, n = 5, $P < 0.001$ vs. control). 7-Hydroxymitragynine (300 nM) did not affect the concentration-response curve for acetylcholine in the ileum (data not shown). These results suggest that 7-hydroxymitragynine has an opioid agonistic activity in the guinea-pig ileum.

Effect of 7-hydroxymitragynine on opioid-receptor binding in brain

Competition binding assays revealed that 7-hydroxymitragynine bound to opioid receptors in homogenates of guinea-pig brain membrane (Table 1). The affinities of these compounds for three opioid receptor types were determined by evaluating the inhibition of binding of ligands to μ-, δ- and κ-opioid receptors. Specific bindings of these radioligands for the opioid receptor types were saturable, and Scatchard plots were linear. The K_D values of [^{3}H]DAMGO, [^{3}H]DPDPE and [^{3}H]U69593 were 1.07 ± 0.06, 0.66 ± 0.05 and 0.87 ± 0.05 nM, respectively. Further, their B_{max} values were 88.2 ± 15, 41.2 ± 0.74 and 78.5 ± 9.8 fmol/mg protein, respectively.

Fig. 3 shows displacement curves for specific binding of [^{3}H]DAMGO, [^{3}H]DPDPE and [^{3}H]U69593 with various concentrations of 7-hydroxymitragynine. 7-Hydroxymitragynine interacted with all three

Table 1
Binding affinities (pKi) of 7-hydroxymitragynine on μ-, δ- and κ-opioid receptors in homogenates of guinea-pig brain

	$[^3H]$DAMGO (μ-sites)	$[^3H]$DPDPE (δ-sites)	$[^3H]$U69593 (κ-sites)
7-Hydroxymitragynine	8.01 ± 0.03	6.84 ± 0.12	6.71 ± 0.11
DAMGO	8.73 ± 0.04	ND	ND
Naltrindole	ND	8.61 ± 0.01	ND
U-69593	ND	ND	8.77 ± 0.03

The values are expressed as the mean ± s.e.mean of five or six separate displacement curves, each assayed in triplicate. The μ-binding sites were labeled with $[^3H]$DAMGO (3 nM), δ-sites with $[^3H]$DPDPE (1 nM) and κ-sites with $[^3H]$U69593 (3 nM). ND: not determined.

opioid sites but bound preferentially to μ-opioid receptors with pKi values of 8.01 ± 0.03, and displayed about 5 times lower affinity than DAMGO (pKi values of 8.73 ± 0.04). The relative affinities of 7-hydroxymitragynine for μ-, δ- and κ-opioid receptors were 89.8%, 5.6% and 4.6%, respectively.

Antinociceptive effects of subcutaneously and orally administered 7-hydroxymitragynine in mice

Antinociceptive effects of 7-hydroxymitragynine and morphine were compared in acute thermal pain tests in mice. Fig. 4 shows the antinociceptive effects of subcutaneous administration of these compounds. The administration of 7-hydroxymitragynine induced antinociception in a dose-dependent manner (2.5–10 mg/kg) in both tests. In the tail-flick test, the MPE value of 7-hydroxymitragynine (5 mg/kg, s.c.) reached 100% between 15–30 min after its administration. On the other hand, the maximum

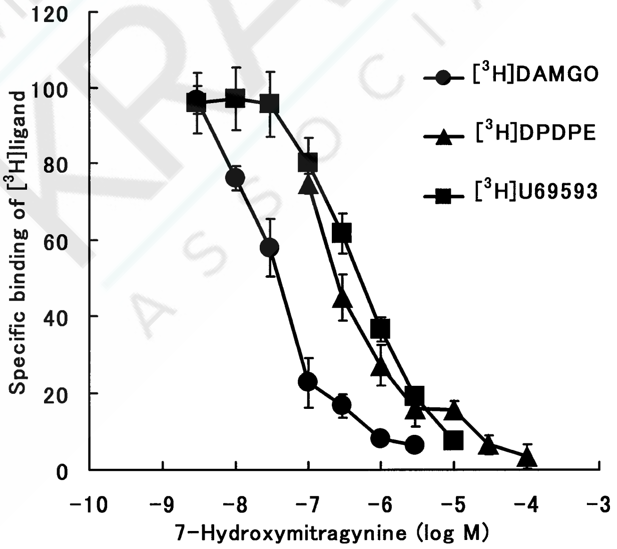


Fig. 3. Displacement curves for 7-hydroxymitragynine on specific binding of $[^3H]$DAMGO, $[^3H]$DPDPE and $[^3H]$U69593 in guinea-pig brain homogenates. Each value is expressed as a percentage of the specific binding in the absence of 7-hydroxymitragynine. Data represent mean ± s.e.mean of five or six separate experiments performed in triplicate.

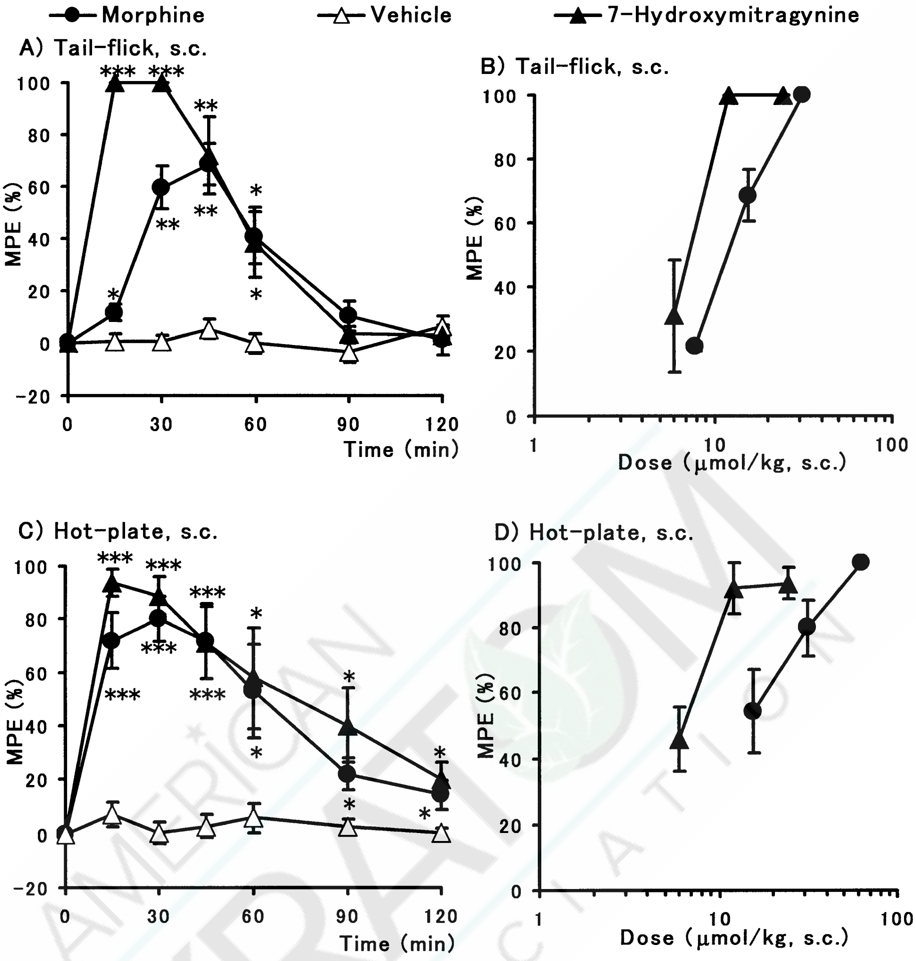


Fig. 4. Antinociceptive effects of 7-hydroxymitragynine and morphine in mice. All compounds were administered subcutaneously. A) Time course of the antinociceptive effect of 7-hydroxymitragynine (5 mg/kg) and morphine (5 mg/kg) in the tail-flick test. B) Dose-response curves for antinociceptive effects of 7-hydroxymitragynine and morphine in the tail-flick test. Each point represents maximum effect of the drugs at each dose. C) Time course of the antinociceptive effect of 7-hydroxymitragynine (10 mg/kg) and morphine (10 mg/kg) in the hot-plate test. D) Dose-response curves for the antinociceptive effect of 7-hydroxymitragynine and morphine in the hot-plate test. Each point represents maximum effect of the drugs at each dose. Each point represents the mean ± s.e.mean of six mice. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, versus the corresponding control group.

MPE value of morphine (5 mg/kg, s.c.) was only about 69% at 45 min after its administration. In the hot-plate test, a similar effect of 7-hydroxymitragynine was observed. The MPE values of 7-hydroxymitragynine (10 mg/kg, s.c.) and morphine (10 mg/kg, s.c.) peaked at 94% at 15 min and 79% at 30 min, respectively, after their administration. The effect of 7-hydroxymitragynine was more efficacious than that of morphine at the same dose in both tests. Naloxone (2 mg/kg, s.c.) inhibited the antinociceptive effect of 7-hydroxymitragynine (10 mg/kg, s.c.) in tail-flick (control, 100 ± 0%, n = 6; naloxone, 8.4 ± 4.9%, n = 6, $P < 0.001$) and hot-plate tests (control, 94 ± 5.0%, n = 6; naloxone, 9.5 ± 4.9%, n = 6, $P < 0.001$).

The results about oral administration are noteworthy in tail-flick and hot-plate tests. Fig. 5 shows the antinociceptive effects of oral administration of 7-hydroxymitragynine and morphine. In the tail-flick test, 7-hydroxymitragynine (2.5–10 mg/kg, p.o.) showed a dose-dependent inhibition of pain response. The MPE value of 7-hydroxymitragynine (10 mg/kg, p.o.) reached 100% between 15–30 min after its administration, and a significant antinociceptive effect lasted for 90 min. On the contrary, the MPE value of morphine (20 mg/kg, p.o.) was only about 49% at 45 min after administration. In the hot-plate test, the MPE value of 7-hydroxymitragynine (20 mg/kg, p.o.) reached 87% at 15 min after administration. In

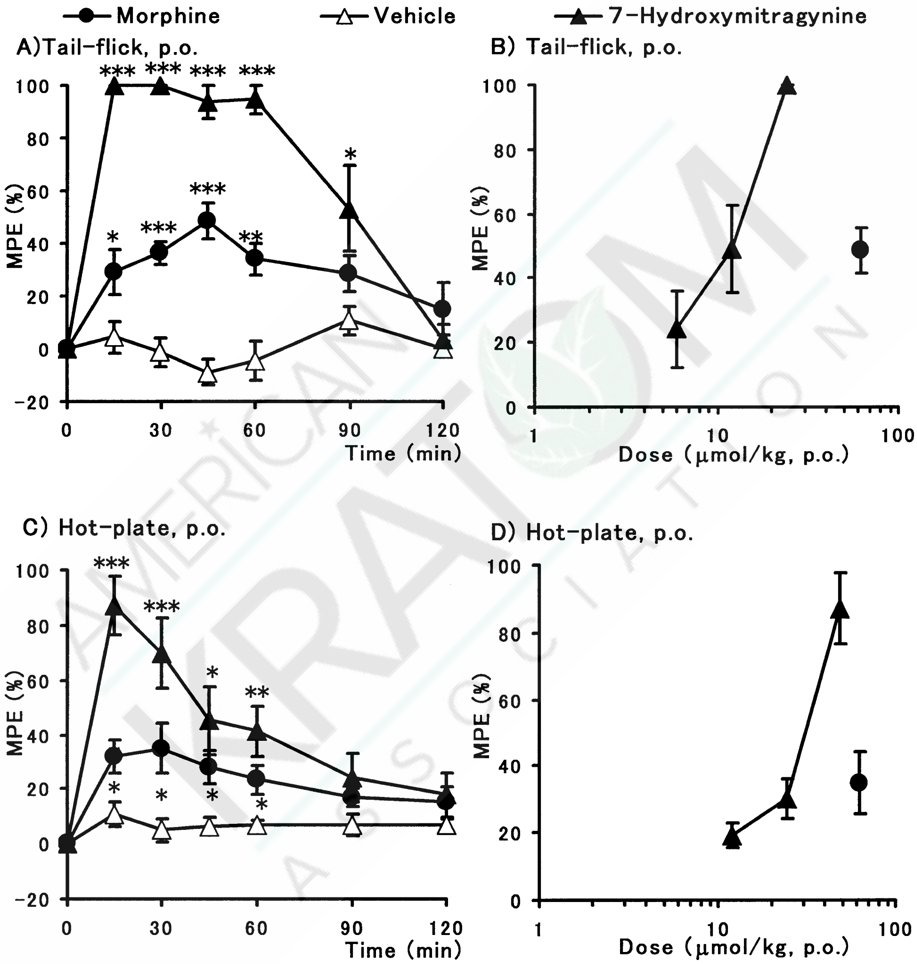


Fig. 5. Antinociceptive effects of 7-hydroxymitragynine and morphine in mice. All compounds were administered orally. A) Time course of the antinociceptive effect of 7-hydroxymitragynine (10 mg/kg) and morphine (20 mg/kg) in the tail-flick test. B) Dose-response curves for antinociceptive effects of 7-hydroxymitragynine and morphine in the tail-flick test. Each point represents maximum effect of the drugs at each dose. C) Time course of the antinociceptive effect of 7-hydroxymitragynine (20 mg/kg) and morphine (20 mg/kg) in the hot-plate test. D) Dose-response curves for the antinociceptive effect of 7-hydroxymitragynine and morphine in the hot-plate test. Each point represents maximum effect of the drugs at each dose. Each point represents the mean ± s.e.mean of six mice. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, versus the corresponding control group.

contrast, only weak antinociception was observed when morphine was orally administered at a dose of 20 mg/kg.

Discussion

We isolated a new compound, 7-hydroxymitragynine, as a minor constituent of the Thai medicinal herb *Mitragyna speciosa* (Ponglux et al., 1994). In the present study, we investigated its opioid effects in an isolated ileum contraction test, a receptor binding assay and antinociceptive tests, and found it to be a potent opioid agonist.

The electrically stimulated ileal preparation from guinea-pig was used as a model of the action of 7-hydroxymitragynine in its putative strong analgesic effects in mice. As morphine did, 7-hydroxymitragynine inhibited the electrically stimulated ileum contraction in a concentration-dependent manner as reported previously (Takayama et al., 2002). On the other hand, 7-hydroxymitragynine did not affect contraction induced by direct stimulation of the receptor on the smooth muscle by acetylcholine. Taken together, it is supposed that 7-hydroxymitragynine acts on the nerve endings to inhibit the release of neurotransmitters. The guinea-pig ileum contains populations of functional μ- and κ-opioid receptors (Lord et al., 1977; Chavkin and Goldstein, 1981). The inhibitory effect of 7-hydroxymitragynine was antagonized by the opioid receptor antagonist naloxone. Taken together, 7-hydroxymitragynine is found to have an opioid agonist property on μ- and/or κ-opioid receptors. In this ileum test, 7-hydroxymitragynine exhibits about 13-fold higher potency than morphine as reported previously (Takayama et al., 2002). It is noteworthy that 7-hydroxymitragynine, a novel alkaloid structurally different from the other opioid agonists, has a more potent opioid agonistic effect than morphine in guinea-pig ileum. In addition, 7-hydroxymitragynine exhibits about 46-fold higher potency than mitragynine as reported previously (Takayama et al., 2002). It is supposed that the introduction of a hydroxy group at the C7 position in the chemical structure of mitragynine is a suitable functional group for pharmacophore binding to opioid receptors.

Guinea-pig brain homogenates are commonly used as means of assessing the multiple opioid receptor binding spectra of narcotic analgesics. A close correlation between in vitro functional systems and opioid receptor binding in the brain has also been suggested (Pert and Snyder, 1973; Lord et al., 1977). Competition binding assays revealed that 7-hydroxymitragynine bound to opioid receptors in homogenates of guinea-pig brain membrane. Its affinities for three opioid receptor types were determined by evaluating the inhibition of binding of ligands to μ-, δ- and κ-opioid receptors. As a result, 7-hydroxymitragynine interacted with all three opioid sites, but bound preferentially to μ-opioid receptors as reported previously (Takayama et al., 2002).

The antinociceptive effect of mitragynine on noxious mechanical and thermal stimulation has been already reported in the tail-pinch and hot-plate tests in mice (Matsumoto et al., 1996a,b; Tohda et al., 1997; Thongpradichote et al., 1998; Watanabe et al., 1999), although its antinociceptive effect was less potent than that of morphine. In the present study, we found potent antinociceptive action of 7-hydroxymitragynine on thermal stimulation in tail-flick and hot-plate tests. The afferent nociceptive stimulus is similar in both tail-flick and hot-plate tests. However, spinal transection of the animal abolishes the pain response in the hot-plate test, while the pain response in tail-flick test is not affected. Therefore, the former is considered to be a supraspinally mediated response, and the latter response is considered a spinally mediated one (Yaksh, 1999).

7-Hydroxymitragynine showed a dose-dependent antinociceptive action when subcutaneously and orally administered to mice. The antinociceptive effect of 7-hydroxymitragynine was more potent than morphine in tail-flick and hot-plate tests in mice. Furthermore, the inhibitory effect of naloxone on antinociception induced by 7-hydroxymitragynine in mice indicates the involvement of opioid receptor systems in its action. Taken together, 7-hydroxymitragynine elicited antinociception in mice through its action on supraspinal and/or spinal opioid receptors. We demonstrated for the first time that 7-hydroxymitragynine has opioid receptor agonistic action sufficiently potent to produce antinociception. It is reported that pseudo-akuammigine, an alkaloid from *Picralima nitida* with structural similarity to mitragynine, exerts antinociceptive activity by oral administration in the tail-flick test (Menzies et al., 1998; Duwiejua et al., 2002).

It is noteworthy that 7-hydroxymitragynine possesses a potent antinociceptive action after oral administration in tail-flick and hot-plate tests. On the contrary, orally administered morphine did not show antinociceptive effects in either test. These results suggest that 7-hydroxymitragynine may be well absorbed when given by the oral route. It is well known that morphine, administered orally, is rapidly metabolized in the liver and excreted in urine (Iwamoto and Klaassen, 1977; Glare and Walsh, 1991). Consequently, a large amount of morphine is orally administered in the clinical use as analgesics. However, the repeated administration of morphine leads to induction of tolerance, and high doses of morphine may elicit undesirable side effects.

Conclusion

The Mitragyna alkaloid, 7-hydroxymitragynine induced dose-dependent antinociceptive effects in tail-flick and hot-plate tests in mice. This compound is structurally different from other opioid agonists, and has a more potent antinociceptive activity than morphine, especially with oral administration. 7-Hydroxymitragynine may be a seed for new analgesics due to its unique structure and a potent activity.

Acknowledgements

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Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation

November 28, 2016

Contents

List of In-Text Tables 4
List of Abbreviations 5
1 Summary, Interpretation, and Discussion of Abuse Potential Data 13
2 Analysis of Kratom under the CSA 8 Factors 21
3 Review of the Eight Factors of the Controlled Substances Act 21
  3.1 Factor 1: Its actual or relative potential for abuse 21
    3.1.1 Animal Data on Drug Discrimination and Reinforcement 23
    3.1.2 Summary of Factor 1 30
  3.2 Factor 2: Scientific evidence of its pharmacological effect, if known 31
  3.3 Factor 3: The state of current scientific knowledge regarding the drug or other substance 33
  3.4 Factor 4: Its history and current pattern of abuse 35
    3.4.1 History 35
    3.4.2 Federal Surveys 37
    3.4.3 Other Federal Data Sources 38
  3.5 Factor 5: The scope, duration, and significance of abuse 40
    3.5.1 Internet monitoring 41
    3.5.2 Dr. Oliver Grundmann Preliminary Report on Kratom Use and the Health Impact of Kratom Consumption – An online anonymous survey 44
    3.5.3 Testimonials Regarding Benefits 46
  3.6 Factor 6: What, if any, risk there is to the public health 46
    3.6.1 American Association of Poison Control Centers' National Poison Data System (AAPCC-NPDS) 48
    3.6.2 Pediatric/Child (less than 6 years of age) exposure related adverse events and deaths. 48
    3.6.3 Ex-US Safety/Toxicity Data 51
    3.6.4 Deaths Possibly Involving Kratom 52
  3.7 Factor 7: Its psychic or physiological dependence liability 55
  3.8 Factor 8: Whether the substance is an immediate precursor of a substance already controlled under this subchapter 56
4 Recommendation 56
5 Conclusion 65
6 References 65
Attachment A: Testimonies of Kratom Consumers 75

List of In-Text Tables

Table 1. Number of units that would be required to achieve discrimination and reinforcement from several over-the-counter products. 26
Table 2. Number of Unweighted Cases of Kratom, Aspirin and Diphenhydramine Reported to the National Survey on Drug Use and Health, 2010-2014. 38
Table 3. National Semiannual Estimates of Selected Opiate and Related Drug Reports in NFLIS, 2009-2014. 40
Table 4. Verbatim accounts from Internet reports from a website that typically attracts people with histories of diverse substance use and abuse to describe their experiences 41

List of Abbreviations

Abbreviation	Definition
7-OH-MG	7-Hydroxymitragynine
8FA	Summary Analysis of the 8 Factors
AAPCC-NPDS	American Association of Poison Control Centers' National Poison Data System
AKA	American Kratom Association
APA	American Psychiatric Association
CA2+	Calcium
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CNS	Central Nervous System
CPP	Conditioned Place Preference
CSA	Controlled Substances Act
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
DHHS	Department of Health and Human Services
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC_{50}	Median Effective Concentration
E_{max}	Maximal Efficacy
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
FOIA	Freedom of Information Act
g	Gram
GI	Gastrointestinal

Abbreviation	Definition
h	Hour
i.p.	Intraperitoneal
IC_{50}	Inhibitory Concentration of 50%
kg	Kilogram
MeOH	Methanol
mg	Milligram
MG	Mitragynine
MTF	Monitoring the Future
N	Number
N/A	Not Applicable
NEISS-CADES	National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance
NFLIS	National Forensic Laboratory Information System
NIDA	National Institute on Drug Abuse
nM	Nanomolar
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
NSDUH	National Survey on Drug Use and Health
p.o.	By Mouth, Orally
s.c.	Subcutaneously
SAE	Serious Adverse Event
SE	Southeast
SG	Surgeon General
SR	Sustained Release
TEDS	Treatment Episode Datasets
THC	Tetrahydrocannabinol
US or U.S.	United States

Abbreviation	Definition
USC	United States Code
δ	Delta
κ	Kappa
μ	Mu
μM	Micromolar

Definitions

Term	Definition
Abuse potential (liability)	Abuse potential, often referred to as abuse liability, is the term used to describe the risk that a substance carries for sustaining self-administration due to central nervous system effects that are typically reinforcing and often pleasant, yet associated with harm. From a regulatory perspective abuse potential is evaluated by 8 factors listed in the Controlled Substances Act (CSA) for the purpose of determining if a substance or drug meets criteria for placement in the CSA and regulation as a controlled substance. In that case, the level or severity of abuse potential is a factor in determining how restrictively a substance or new drug should be regulated. Many substances that are not placed in the CSA have noteworthy levels of abuse potential, e.g. caffeine, nicotine, nutmeg, various antihistamines, glues, whipped-cream aerosols, salvia, and dextromethorphan (active ingredient in many cough suppressants) (Hanson, 2014; See discussion in FDA 2010b and NIDA, https://www.drugabuse.gov/publications/finder/t/160/DrugFacts).
Addiction	Addiction is often used interchangeably with terms such as dependence and substance use disorder (see further on in definitions). Addiction is generally defined as a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. This definition of addiction has been accepted by the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine. See also O'Brien, 2011. The National Institute on Drug Abuse (NIDA) focuses more on the research and mechanisms of addiction in its definition. It defines addiction as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences. It is considered a brain disease because drugs change the brain—they change its structure and function. These brain changes can be long-lasting, and can lead to the harmful behaviors seen in people who abuse drugs.

Term	Definition
	NIDA, and many others, consider addiction to be equivalent to a severe substance use disorder as defined in the APA DSM-5 (see https://www.drugabuse.gov/publications/media-guide/science-drug-abuse-addiction-basics).
Eight Factors of the CSA which must be analyzed for scheduling recommendations	(1) Actual and relative potential for abuse (2) Scientific evidence of its pharmacological effects (3) State of the current scientific knowledge regarding the drug (4) History and current pattern of abuse (5) Scope, duration, and significance of abuse (6) Public health risk (7) Psychic or physiologic dependence potential (8) Whether the drug is an immediate precursor of a controlled substance
Controlled Substances Act Drug Schedules	Placement of a substance in the CSA is often referred to as being “scheduled” because it must be placed in one of the five drug schedules based on the 8-Factor Analysis of the CSA. Schedule I (C-I): Substances that do not have an accepted medical use and have a high abuse potential and/or were designated for C-I in the 1970 CSA, e.g., heroin, LSD, GHB, “bath salts,” cannabis. Special DEA license and other requirements are required for research. Schedules II-V: For substances (drugs) that have an accepted medical use (typically approved for medical use by the FDA). C-II is for substances with the highest abuse and physical dependence potential and overall risk characterization; C-V is for substances with the lowest abuse potential and lowest dependence potential and risk. C-II includes morphine, amphetamine, pentobarbital, methadone, oxycodone, nabilone, phencyclidine. C-III includes buprenorphine, ketamine, secobarbital, Xyrem, dronabinol, chlorphentermine. C-IV includes tramadol, diazepam, phenobarbital, mazindol, pentazocine, sibutramine, butorphanol. C-V includes low dose codeine, lacosamide, pregabalin.
Kratom	A plant of the species *Mitragyna speciosa*, including its leaves, and any product derived solely from this plant, including kratom powder and tea brewed from kratom. Two alkaloid components of kratom are MG and 7-OH-MG. Scheduling either or both of these alkaloids under CSA would also have the effect of

Term	Definition
	controlling kratom and kratom products. In this analysis, the term "kratom" will be used as the umbrella term to refer to the plant product, its extracts, MG, 7-OH-MG, and/or manufactured products that include any of the foregoing, unless more specific terms (e.g., "MG" or "leaves") are used.
Substance Use Disorder (Drug Dependence)	"Substance Use Disorder" formerly termed "Dependence" by the APA is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems. Substance Use Disorder requires a pattern of repeated self-administration that can result in tolerance, withdrawal, and compulsive drug taking behavior. Specific diagnostic criteria are listed in the DSM-5 (APA, 2013). DSM-III and DSM-IV had included a less severe form of dependence termed abuse (APA, 1980, 1994) which was discarded in DSM-5.
Overdose or drug poisoning death	At a general level, the term overdose can and is loosely used by individuals, the media, and often health care professionals any time that a substance was used in greater than intended amounts and/or produced undesirable effects attributed to the amount of the substance. Use of the term overdose as a cause of death is unfortunately also often loosely used, and this is not helpful in efforts to document actual cause of death, analyze trends, or guide efforts to control and prevent such effects, particularly if the attribution was incorrect. Many substance-related overdose deaths involve combinations of substances such as alcohol, sedatives, and opioids and it is often not clear which substance should be listed as the primary cause of death (Gudin et al., 2013; Rudd et al., 2016; Ossiander, 2014). Furthermore, other physical conditions and disease states may contribute to death associated with drug administration. Thus, many factors contribute to determining whether a death resulted from sufficient drug exposure to justify considering the death a drug poisoning death, and to which drug or substance the death should be attributed if it is plausible that more than one substance was taken. Forensic toxicology experts and medical examiners recommend a variety of criteria to determine the most appropriate description of the involvement of a substance in the death, but these are not always followed. Thus, deaths attributed in the media as an overdose due to one

Term	Definition
	specific substance on the basis that the substance was present may be incorrectly attributed to overdose. The following categorizations of the nature or level of involvement of a substance in a death are used in many medical examiner and emergency medicine reports: Causative: The substance is unequivocally responsible for illness or death. Probable cause of death: Death is a known complication of the administered substance and the clinical picture is in keeping with previous experience and reports, provided other causes of death have been reasonably eliminated. Possible cause of death: The clinicopathologic picture could be caused by the drug in question, but it could just as easily be caused by some other process found in the decedent; assigning the drug in question as the cause of death would be unique and warrant publication in the medical literature. Coincidental: The substance happens to be present but has no bearing on illness or death. Negative: The substance is not detected. (See discussion in http://emedicine.medscape.com/article/1680257-overview#a9; Cone et al., 2003, 2004; FDA, 2010a).
Tolerance	Tolerance is defined for diagnostic purposes by the APA (2013) as the need for greatly increased amounts of the substance to achieve intoxication (or the desired effect) or a markedly diminished effect with continued use of the same amount of the substance (FDA, 2010a).

Term	Definition
Withdrawal	Withdrawal is defined for diagnostic purposes by the APA (2013) as follows: The essential feature is the development of a substance-specific problematic behavioral change, with physiological and cognitive concomitants, that is due to the cessation or reduction in heavy and prolonged substance use. Withdrawal symptoms, which are generally opposite of the acute effects of the substance, vary greatly across the classes of substance, and separate criteria sets for withdrawal are provide for most classes (FDA, 2010a). Note that pharmacologists generally consider withdrawal signs and symptoms to be the consequence of physical dependence and a measure of physical dependence. Physical dependence is the state of adaptation or neuroadaptation (tolerance) in which relatively normal functioning has come to be dependent upon continued drug administration. This is sometimes described as “the resetting of homeostatic mechanisms in response to chronic drug exposure” (e.g., O’Brien, 1996, 2011). The presence of withdrawal does not necessarily mean that the person was addicted as defined earlier or had a diagnosable substance use disorder by APA DSM-5 criteria. For example, many opioid treated pain patients develop tolerance and physical dependence and must be gradually tapered off their medication to minimize withdrawal discomfort yet show no evidence of craving, drug seeking, or behaviors indicative of substance use disorder or addiction. Furthermore, individuals can become physically dependent on the effects of a drug used for lowering blood pressure (FDA, 2010a) but which do not cause substance use disorders or addiction. Caffeine may cause APA DSM-5 diagnosable intoxication and withdrawal disorders, but the DSM-5 does not include substance use disorder category for caffeine because the clinical significance of chronic caffeine use and diagnostic criteria have not been established (Hasin et al., 2013) as would be needed to distinguish a substance use disorder from a common life-style and or life enhancing behavior.

1 Summary, Interpretation, and Discussion of Abuse Potential Data

We have developed this summary analysis of the eight factors (8FA) of the Controlled Substances Act (CSA) to determine if placement of kratom or its alkaloids, mitragynine (MG) or 7- Hydroxymitragynine (7-OH-MG) in the CSA is warranted, and the impact such placement would have on the public health. Equally importantly, we are developing this review to assist the Food and Drug Administration (FDA), National Institute on Drug Abuse (NIDA), Department of Health and Human Services (DHHS), and Drug Enforcement Administration (DEA) in their efforts to find the most appropriate regulatory framework to permit appropriate use, minimize unintended effects, encourage research, and contribute to the enhancement of public health.

Although MG and 7-OH-MG have sometimes been referred to as “opioids,” in this document the term “opioid” will only be used to refer to molecules and products that are opioids as defined by the CSA, which identifies opioids as substances with addiction-forming or addiction-sustaining liability similar to morphine, or substances capable of conversion into drugs with such liability. *See* 21 USC 802(18); *see also* 21 USC 812(c) (scheduling opium, opium derivatives, and opiates, including opium extracts and derivatives of thebaine); 21 CFR 1308.12 (same). This definition excludes kratom and its alkaloids.[1] It is clear that the abuse potential and harmfulness of kratom and its alkaloids are substantially lower than that of morphine and other opioids and differ in other ways as well, such as physiologic manifestations. In fact, as discussed in this review and in other authoritative reviews, the mitragynines have unique and mixed actions that include mild or “caffeine-like” stimulant effects at low to moderate levels of consumption, and are more likely to enhance occupational performance and social interactions than to interfere with such. In this analysis, the term “kratom” will be used as the umbrella term to refer to the plant product, its extracts, MG, 7-OH-MG, and/or manufactured products that include any of the foregoing, unless more specific terms (e.g., “MG” or “leaves”) are used.

Mitragyna speciosa is a tropical deciduous tree within the coffee family (*Rubiaceae*) that is indigenous to Southeast Asia, particularly Thailand, Malaysia, Indonesia, Philippines, and Vietnam. Traditionally Southeast Asia laborers have used small quantities of kratom throughout the workday for the energizing and minor pain-relieving (minor aches and pains) effects. Kratom has been safely consumed as a dietary supplement, a natural remedy, and in food preparation in Southeast Asia for centuries (Tanguay,

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[1] This is also consistent with DEA’s prior determination that emergency scheduling, reserved for substances other than those already controlled in the CSA, including those defined as opioids, was an available statutory pathway for control of kratom, including MG and 7-OH-MG.

2011). It generally is consumed orally in the form of consumer brewed tea-like preparations and powdered kratom leaves that are placed in the mouth or on other foods and are washed down with a liquid. In Southeast Asia, chewing fresh leaves and sometimes dried leaves is also very common, and there are many variants on liquid preparations and some swallowable semisolid preparations made by consumers and various vendors. There is very little evidence demonstrating kratom use through other routes of administration that predominate for opioids in Southeast Asia (e.g., smoking and injecting) despite the long history of wide-spread consumption of kratom. Similarly, in the US, there is little evidence of kratom consumption in forms other than liquid preparations or powdered leaf material that is swallowed with food or liquids. This is in striking contrast to what has been observed for opioids, stimulants, cannabis, nicotine, and other substances of abuse. In fact, for opioids in particular, FDA has actively sought to incentivize the development of products resistant to tampering due to the common and dangerous practice of tampering with oral opioid medications for abuse by nasal insufflation, smoking, and injecting (FDA, 2015; Schnoll and Henningfield, 2016).

The scientific and ethnographic literature often describes consumption as primarily motivated by the “useful,” “beneficial,” “labor sustaining,” “therapeutic,” “mood” and “well-being” enhancing, and “instrumental” benefits, as well as dependence (Aziz, 2014; Hassan et al., 2013; Ward et al., 2011; Warner et al., 2016). The rates of dependence among kratom users in Southeast Asia are not known; however, as discussed in Factor 5, kratom consumers and others regard the practice as more benign and more likely to enhance occupational demands and social functioning in contrast to opioid use which is generally regarded as impairing occupational and social functions (Aziz, 2014; Hassan et al., 2013; Ward et al., 2011; Warner et al., 2016). There are parallels in reported motivation between consumption of kratom and consumption of coffee, tea, and other caffeinated beverages, which are often reportedly used for sustaining performance and for alerting effects, mood enhancement, weight control, relief of headaches, and other benefits (Addicott, 2014; Borota et al., 2014; Cappelletti et al., 2015; Goldstein et al., 2010; Meredith et al., 2013). As with caffeinated beverages, high dose chronic kratom consumption can lead to use consistent with dependence with difficulty abstaining, as well as apparent withdrawal symptoms. Such high dose chronic consumption of kratom appears to be mostly limited to Southeast Asia and relatively uncommon in the US (e.g., Aziz, 2014; Hassan et al., 2013; Ward et al., 2011; Warner et al., 2016; Goldstein et al., 2010; Meredith et al., 2013).

The intertwining of factors that include consumption for benefit and life-style enhancement along with varying degrees of dependence, whether for caffeinated beverage consumption or kratom consumption, demonstrates the importance of distinguishing between volitional lifestyle and life enhancing consumption, and “dependence” or “addiction.” As is the case with consumption of caffeinated beverages, kratom consumption is not commonly associated with adverse health effects (other than minor gastrointestinal discomfort that serves to limit pleasure and consumption), and thus consumption appears rarely to be occurring “in the face of harm or personal or recurrent social problems,” which is a common defining feature of substance use disorders as defined by the American Psychiatric Association (2013) or by other definitions of drug dependence or addiction (American Psychiatric Association 1994; World Health Organization, 1992; American Society for Addiction Medicine, 2016; National Institute on Drug Abuse, 2016).

These factors taken together for caffeine contribute to the reason that the DSM-5, as in earlier editions, does not formally recognize caffeine substance use disorder even though it includes criteria for diagnosis of caffeine intoxication and withdrawal disorders (APA, 2013). Similarly, whereas the opinion of the authors of this analysis is that kratom, like caffeine, can cause dependence if taken in very large quantities (Henningfield, 2015; Aziz, 2014; Hassan et al., 2013; Lanier et al., 2016; Ward et al., 2011; Warner et al., 2016) and "it also carries some abuse liability" (Ward et al., 2011, p. 1001), at least in the US, consumption is generally considered volitional and for the general and/or specific desired effects associated with consumption, as is the case with caffeinated products (Henningfield, 2015).

Serious substance abusers seem to agree that kratom is not a preferred drug of abuse. Evaluations posted on websites and discussion groups where persons who abuse drugs share information report mild and relatively slowly onsetting effects. Their experiences often include both desired and undesired effects that fall far short of what can be readily produced by prototypic drugs of abuse as discussed in Factor 5 of this report. Consistent with this is the virtual absence of evidence that kratom consumption is a significant or serious public health problem or has emerged as a form of substance abuse on any major national US drug monitoring surveillance system, as summarized in Factors 4 and 6 of this report. The lack of public health problems or abuse is despite the fact that there has been widespread consumption of kratom by consumers for more than two decades in the US, and likely consumption among some populations for decades longer.

After an analysis of available data and information, it is clear that kratom, like caffeine, nicotine, dextromethorphan, many antihistamines, antidepressants, and other substances[2] sold as consumer products and/or as medicines, not to mention various solvents, inhalants, and glues, share limited evidence of characteristics that could be used to support placement in the CSA if that was a predetermined objective. However, such a conclusion would require an extremely selective reading of the evidence that discounts the many mitigating factors in their use patterns. Moreover, whether such substances, including kratom, *should* be so controlled is a more complicated issue and one that must consider the overall public health assessment that is part of the CSA eight factor analysis. There is ample precedent from many other substances and products that share characteristics with certain controlled substances, but have not been placed under the CSA and which are regulated through other statutory and regulatory authorities to promote safe and appropriate consumption and to minimize unintended and harmful effects. These include dextromethorphan, nicotine smoking cessation aids, and caffeine (e.g., Consumer Healthcare Products Association, 2010; Food and Drug Administration, 1995, 1996, 2010b; Henningfield, 2015; Lanier, Fant, Cone, and Henningfield, 2016; Meredith, Juliano, Hughes, and Griffiths, 2013; National Institute on Drug Abuse, 2016a).

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[2] Including alcohol and tobacco, but tobacco products and alcoholic beverages are exempted from CSA scheduling by the 1970 CSA itself. 21 USC 802(6) ("The term 'controlled substance' means a drug or other substance, or immediate precursor, included in schedule I, II, III, IV, or V of part B of this subchapter. The term does not include distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1986.").

This analysis also recognizes that the present situation is different from a typical scheduling analysis for a product developed as a drug for FDA approval. Rather, this analysis must address the evidence concerning various kratom preparations and products that have been used for centuries in Southeast Asia and decades in the US. In the US, there are an estimated several million users purchasing products from more than 10,000 retail outlets with an estimated annual market of 207 million dollars (Botanical Education Alliance, 2016). Consumers include immigrants and their families from Southeast Asia where consumption is widespread as a natural remedy and in traditional food preparation. Anecdotal evidence suggests that such consumption has existed in the US for several decades. The more general consumption across the US has largely developed in the past two decades.

The purpose of this document is to review the data related to the abuse potential and toxicity of *Mitragyna speciosa* (also known as kratom) and its primary alkaloids, mitragynine (MG) and 7-hydroxy-mitragynine (7-OH-MG), and the relevance of those data to the doses found in kratom.

Following is a summary of the main conclusions of this analysis and recommendation:

1) Placement of kratom in the CSA is not warranted from a public health perspective and is more likely to cause public health problems that do not presently exist.

2) Kratom consumption has not emerged as a public health or medical problem for adults or children despite more than two decades of rapidly increasing consumption by millions of Americans served by approximately 10,000 vendors. Specifically, among the 3-4 publicly documented deaths that have ever been suspected to possibly have involved the consumption of kratom, none have been shown to merit designation as a kratom overdose death and all have involved either other substances or physical or mental health conditions that may have been the primary causes of, or significant contributors to, the death. Remarkably, no deaths, serious adverse effects, or emergency department

exposures have been reported in children. It is important to understand that this conclusion does not mean that such events have never or will never occur, but the signal for a public health problem associated with kratom marketing and consumption is very weak.

3) Appropriate regulation of kratom products, whether natural or processed leaves, or manufactured derivatives marketed as dietary supplements, is as important for kratom as it is for products such as coffee, tea, and related extracts that are currently regulated under existing Food, Drug, and Cosmetic Act (FDCA) authority.

4) Kratom consumption is widespread across the US and spans more than two decades, but kratom consumption has not emerged as a substance abuse problem in the US as measured by any of the US national substance abuse monitoring surveillance systems or by our nation's networks of substance abuse treatment programs that are constantly adapting to the challenges posed by those seeking treatment for emerging forms of abuse and dependence.

5) Current kratom users report being likely to be adversely affected and possibly motivated to seek illicit sources if lawfully marketed kratom were no longer available. This would seem likely to include many Southeast Asian immigrants who are believed to have brought kratom consumption customs with them to the US; however, there has been very little documentation and characterization of kratom use patterns in the US by such populations.

6) Kratom consumption appears to be primarily motivated by its perceived effects that enhance well-being, occupational performance, and social interactions, as well as serving as a natural "home remedy" that is preferred by millions of Americans to conventional medicines.

7) The foregoing is consistent with the pharmacology of kratom and more specifically its alkaloids (MG and 7-OH-MG), which produce mixed pharmacological effects that are generally mild and caffeine stimulant-like at lower dosages. Consumption does not typically interfere with work or social activities and commitments, and in fact kratom is widely reported in the US, as in Southeast Asia, to contribute to work productivity, quality of life, and social relationships.

8) The primary effects of kratom are likely predominantly produced by MG with possible contribution of 7-OH-MG. These two alkaloids have been characterized as including partial mu opioid receptor activity including anti-nociception (pain relief), mild pleasurable effects, and constipation at high doses but an apparent lower risk of constipation at typical levels of consumption as compared to opioids. Respiratory depressant effects appear substantially lower than those produced by opioids – a finding that would be consistent with the absence of verified

kratom caused overdose deaths. Future research should study the respiratory effects of kratom in combination with known respiratory depressants because the absence, or at least very low apparent risk, of kratom overdose poisoning suggests that the effects of such depressants are not substantially enhanced by kratom.

9) Injection of very high doses of MG can produce discriminative stimulant and opioid-type reinforcement in rodents; however, these effects only occur at doses that appear far higher than those that could be ingested in a single sitting by humans, and the relevance of such findings to human oral kratom consumption is not clear. In fact, the doses of MG required to produce discriminative stimulant effects and reinforcement in rodents are much higher than the doses that could be easily ingested from kratom. This is in contrast to many other consumer products, including dextromethorphan and nutmeg, in which it is relatively easy to consume enough doses to achieve a reinforcing and/or intoxicating effect.

10) In contrast to the effects of increasing the dose of substances of high abuse potential (e.g., opioids, stimulants, and sedatives), increasing the dose of kratom is more likely to produce undesirable gastrointestinal effects, constipation, and lethargy, and little additional mood enhancement. More research is needed to better characterize the profile and understand the mechanisms of action of kratom.

11) Animal studies have demonstrated some signs consistent with physical dependence and withdrawal at what appear to be extraordinarily high dosages of MG. Specifically, laboratory rats were given 30 mg/kg/day i.p., equating to an oral dose of about 990 mg/kg (Yusoff et al., 2016). Humans would need to consume over 800 oral doses of kratom in a single sitting to achieve the same dose of MG. In fact, no evidence has demonstrated production of physical dependence and withdrawal at levels consistent with human use. However, the modest desirability of the effects would seem to make such a heroic effort extremely unlikely because the pleasure derived from consumption does not appear similar in magnitude to that produced by far less costly and readily available doses of typical substances of abuse including marijuana, alcohol, stimulants, sedatives, and opioids. More research is needed to understand the relevance of such findings to human consumption and better characterize kratom among other substances.

12) MG and kratom have very low toxicity, and thus a favorable safety profile. There have been few reports of serious adverse events or deaths associated with kratom and for most, the contribution of kratom is not clear. For example, in Sweden in about 2008-2009, a blend of herbals including kratom along with the opioid analgesic O-desmethyltramadol, and possibly co-administration of other drug substances was associated with nine deaths. Tramadol (including O-desmethyltramadol), in contrast to kratom, has been documented to carry a risk

of severe respiratory depression and overdose death. To date, in the US, there have been no confirmed reports of death that can be considered “causatively” due to kratom overdose. How many, if any deaths, are “probably” classified as kratom poisoning deaths is not clear. This is consistent with the far larger and longer Southeast Asian experience of very few serious adverse events. In both the US and Southeast Asia, the low toxicity of kratom is in striking contrast to the experience with opioids.

13) With respect to safety, the absence of reports of adverse effects associated with pediatric exposure to kratom is striking given that children under six years of age are considered highly vulnerable and account for many poison control center calls and emergency department visits from exposure to a broad range of household products, over the counter drugs, and prescription drugs including opioids. The total absence of reports of adverse effects in children likely seems due to a combination of the low toxicity of kratom, the distastefulness of the products, and the relatively low concentrations of alkaloids in personal and commercial preparations.

14) Taking together basic research findings, available epidemiology, clinical observations, and anecdotal self-reports, very high levels of chronic intake of kratom can cause signs consistent with physiological dependence and withdrawal and some degree of psychological dependence, although any signs consistent with dependence have not been accompanied by use through harm or social detriment. However, in many respects, the factors that appear important in sustaining kratom consumption appear more similar to those that sustain dietary caffeine consumption, namely to better manage fatigue and daily life demands and provide mild effects considered enhancing to quality of life. Further research should help to better characterize kratom as it compares to other substances that affect behavioral and physiological function and the contribution of such effects to consumption and safety.

15) There has been little study of the rates, risk, or nature of what might be categorized as a substance use disorder involving kratom in the United States. Anecdotal data, including the testimonials appended to this report, suggest that most use is for life-style enhancement and as a natural remedy for various ailments. Thus, rather than consumption to sustain addiction or to get high, and with little apparent harm to self or others, consumption appears largely to the benefit of individuals. This suggests a similarity with caffeine containing products that certainly can produce dependence and withdrawal but which have not been recognized for a disorder category of dependence or substance use disorder category by the American Psychiatric Association (APA, 2013) because there has not been sufficient documentation of clinical impairment or use despite harmful effects.

16) In addition, the partial mu agonist activity of two alkaloids, MG and 7-OH-MG, likely confers some degree of relief of at least minor pain, diarrhea, and coughing, and it is plausible, predicting from what is known of the pharmacology, that high dosages could provide some relief of symptoms of opioid withdrawal; however there has been little systematic study of such potential benefits.

17) There appear to be remarkably low risk of serious adverse effects from kratom consumption as compared to opioids and other common drugs of abuse. Further, there is little evidence that kratom products are used by routes other than oral beverage or food consumption. In contrast, opioids and many other drugs of abuse are frequently used by high impact routes such as nasal insufflation, smoking, and injecting. Graduation from oral consumption to such other routes is common for opioids and other substances of abuse but not for kratom.

18) Although the primary alkaloids of kratom, MG and 7-OH-MG, may demonstrate some characteristics considered for controlled substance scheduling, as do many other products including caffeine, nicotine, some antihistamines, and alcohol, despite decades of wide-spread consumption, there does not appear to be a public health risk that would warrant their scheduling.

19) Consumption of kratom products appears to provide positive benefits such as relief of pain and fatigue without the adverse consequences produced by other products that are used for similar purposes as reported in the appended testimonials and over a century or more of documented consumption in Southeast Asia. For example, liver disease caused deaths associated with the use of acetaminophen is a serious problem in the US, and there are problems of serious GI side effects and cardiovascular problems associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDS). At the far extreme, there is the inherent risk of overdose and serious addiction associated with the use of opioids. For those who manage various ailments with kratom instead of such products, the benefit to risk ratio appears favorable.

20) Banning or restricting access to kratom products would not only deny current kratom consumers of the benefits they obtain from kratom, but would likely serve to create a substantial illicit market to meet those demands. This illicit market would not be subject to regulation such as by the FDCA and would be more likely to harm public health than to maintain appropriate access through the lawfully regulated marketplace. Schedule I placement would not only restrict access to consumers, it would also severely impede the willingness and ability of researchers to conduct the research that is vital to more thoroughly characterizing the effects, mechanisms of action, and safety of kratom. Keeping appropriately regulated kratom products available in the US appears to be in the interests of public health.

2 Analysis of Kratom under the CSA 8 Factors

The present 8-factor analysis has been developed to determine the appropriateness of CSA scheduling of kratom and/or its alkaloids and derivative products, and if so, the most appropriate schedule for kratom.

Based on all lines of evidence considered in the 8-factor analysis, kratom's potential for abuse, tolerance, and dependence is lower than that of many schedule IV and V drugs and is well within the range of many nonscheduled drugs and substances (e.g., caffeine, nasal nicotine spray, fluoxetine, bupropion, dextromethorphan). Although kratom and its primary alkaloids MG and 7-OH-MG share certain characteristics with controlled substances, as do many nonscheduled substances, there does not appear to be a public health risk that would warrant control of kratom products or their alkaloids under the CSA. Rather, regulation under the FDCA by the FDA would seem the most effective mechanism to ensure continued access to kratom products that are marketed with appropriate oversight.

3 Review of the Eight Factors of the Controlled Substances Act

3.1 Factor 1: Its actual or relative potential for abuse

Definitions of addiction, abuse potential, and other terms, which are provided at the beginning of this report, are important to understand the following analysis. There is no question that consumption of kratom can produce effects that, at least at some doses, people can feel and which are important in their decision to consume kratom. Analysis of Factor 1 will provide part of the basis for characterizing its effect profile with respect to the nature and strength of the effects and the relevance of this for a scheduling recommendation.

Perhaps the most prevailing observations in clinical, scientific, and ethnographic reports from 1930 to 2016 about the reasons for kratom consumption are the functional benefits of kratom consumption to enhance and sustain, if not enable occupational work demands, and as a social interaction enhancer when used together with family and friends. Hassan et al. (2013) attribute most kratom consumption as at least initially motivated by what they, and others, term "instrumental" or "instrumentalized" consumption as a means of achieving work goals and not withdrawing from such obligations.

There is also agreement that at least in Southeast Asia, abuse, dependence, and/or addiction may develop with heavy daily consumption, at least among hard laborers, as seems historically more prevalent there than in the United States, but with the recurrent explanation that this seems heavily driven by work and environmental demands and that, in contrast to daily opioid use (when such comparisons are made), such consumption is more likely associated with beneficial occupational and social outcomes.

More specifically, the scientific and ethnographic literature often describes kratom consumption as primarily motivated by the "useful," "beneficial," "labor sustaining," "therapeutic," "mood" and "well-being" enhancing, and "instrumental" benefits, as well as dependence (Aziz, 2014; Hassan et al., 2013; Ward et al., 2011; Warner et al., 2016). There are parallels in reported motivation for consumption of coffee and tea and other caffeinated beverages which are often reported as used for sustaining performance, alerting effects and enhancing mood (Addicott, 2014; Borota et al., 2014; Cappelletti et al., 2015; Goldstein et al., 2010; Meredith et al., 2013). As is the case with caffeinated beverages, at least high dose chronic kratom consumption, as appears more common in Southeast Asia than the US, can lead to signs consistent with dependence with difficulty abstaining, as well as apparent withdrawal symptoms (e.g., Aziz, 2014; Hassan et al., 2013; Ward et al., 2011; Warner et al., 2016; Goldstein et al., 2010; Meredith et al., 2013). The intertwining of these factors, for caffeinated product consumption as for kratom product consumption, requires close attention to detail in distinguishing "dependence" without harm or negative social effects from "addiction." In both, only the former has been observed. Another parallel with caffeinated beverages is the fact that common levels of kratom consumption are not commonly associated with adverse health effects. Thus, consumption is not typically "in the face of harm or personal or recurrent social problems" as is a common defining feature of dependence disorders (i.e., "addictive" or "substance use" disorders) as discussed further in this review.

These factors taken together contribute to the reason that the APA DSM-5, as in earlier editions, does not formally recognize caffeine substance use disorder even though it includes criteria for diagnosis of caffeine intoxication and withdrawal disorders (APA, 2013). Similarly, whereas the opinion of the authors of this analysis is that kratom can cause signs consistent with dependence without harm or social problems (Henningfield, 2015; Aziz, 2014; Hassan et al., 2013; Lanier et al., 2016; Ward et al., 2011; Warner et al., 2016) and "it also carries some abuse liability" at very high doses (Ward et al., 2011, p. 1001), at least in the US, consumption is generally considered volitional and for the general and/or specific desired effects associated with consumption as is the case with caffeinated products (Henningfield, 2015). Both products' volitional use is not consistent with abuse of the product or a dependence disorder.

The apparent worst case scenario conditions for very heavy consumption appears to have been in Southeast Asia among laborers who were required to work at heavy labor tasks for long hours and often in extremely high heat conditions. Kratom leaves were plentiful and heavily relied upon to enable such work. This was described in 1930, in *The Chemist and the Druggist*, in a short article titled, "Kratom Eaters" that described the effects of chewing 10-30 kratom leaves three times per day by laborers to prolong their ability to be capable of "arduous work" including improved tolerance to endure fatigue and "torrid heat" (Available at https://archive.org/stream/b19974760M2738/b19974760M2738_djvu.txt, accessed November 28, 2016). Note that this quantity of kratom appears extremely high compared to typical kratom consumption, however, the article included no estimate of alkaloid content or nature of the leaves that would permit quantitative comparison to today's products and practices. Nonetheless, these kratom consumers were considered to be "addicted" by the author, but that definition is not consistent with the contemporary use of the term because, as noted by the author, "the habit is stated not to be harmful since the kratom eater does not change his character."

Aziz (2014) also credited kratom consumption primarily by workers to increased endurance and stamina, as well as for social reasons. Singh et al. (2014), in a review of dependence and potential withdrawal, also described very heavy consumption among workers but also by many people as a social enhancer with family and friends, with about 79% of such consumers using daily. They stated that “Most users share the belief that it is better to consum[e] Kratom in order to improve work performance than using illicit stimulant-drugs which could also be more expensive.” It was observed that in contrast to the view of opioid users, kratom users were seen as “diligent” and “hardworking” despite the view that they were dependent and many experienced mild symptoms consistent with withdrawal upon termination of use. Similarly, Suwanlert (1975) described “regular kratom users” as having an increased tolerance for work and “increased calm.”

Taken together these observations suggest that consumption is more analogous to the consumption of caffeinated products that makes daily caffeinated beverage consumption so common in the US and globally. These observations are not the pattern of the adverse effects of prototypic addictive drug use on life, health, and society.

3.1.1 Animal Data on Drug Discrimination and Reinforcement

3.1.1.1 Discrimination

Drug discrimination procedures have often been used to help characterize the central nervous system (CNS) effects and predict the abuse potential of new drugs (Ator and Griffiths, 2003), and there is a strong positive relationship between discriminative stimulus effects of drugs in non-humans and the subjective effects of the same drugs in humans (Lelas et al., 2000; McMahon et al., 2002). However, generalization with an active substance known to cause dependence in itself is not necessarily indicative of dependence potential (Ator and Griffiths, 2003). Rather, the results should indicate whether or not kratom and/or its constituent compounds are likely to have subjective effects that are qualitatively similar to that of prototypic drugs of abuse.

There have been no studies of the discriminative stimulus effects of kratom as an herbal product. However, as discussed below, there has been a study of the discriminative stimulus effects of injected MG which showed that doses that would appear extremely large (e.g., an equivalent of over 500 2-ounce bottles of one widely marketed product (VivaZen®) if taken orally (Henningfield, 2015)) can provide morphine-like effects in rats. The relevance of the findings for human consumption and regulation are extremely limited because, as discussed below, there are virtually no reports of extraction or injection of its alkaloids or consumption by any other route at this level. The research is solely helpful in better understanding the mechanism of kratom’s constituents.

Harun et al. (2015) investigated the discriminative stimulus effects of MG in rats. The pharmacological mechanism of MG action and its derivative, 7-OH-MG, with a specific focus on opioid receptor involvement was examined in rats trained to discriminate morphine from vehicle. Rats acquired the MG discrimination (15.0 mg/kg, i.p.);

however, approximately 100 trials of training (50 MG and 50 vehicle sessions) were required before the rats could discriminate MG from vehicle. The group of rats trained to discriminate morphine (5.0 mg/kg, i.p.) from vehicle required fewer training trials, i.e. approximately 60 training sessions in total (30 morphine and 30 vehicle). In stimulus generalization tests with a range of MG doses, 3.0 mg/kg, i.p. produced partial generalization to the 15.0 mg/kg, i.p. dose (around 60% MG-appropriate responding), and full generalization to the training dose was found at the 10.0 mg/kg, i.p. dose. MG substituted fully to the morphine discriminative stimulus in a dose-dependent manner, suggesting pharmacological similarities between the two drugs. However, generalization to morphine occurred at the MG dose of 15.0 mg/kg, i.p., and was not seen at the 1 or 3 mg/kg, i.p. dose. This 15 mg/kg i.p. dose would thus equate to an oral dose of about 495 mg/kg[3] in rats to produce an effect that resembles 5 mg of injected morphine. Converting this to a human equivalent dose based on body surface area, this would equate to 79.84 mg/kg in humans, or almost 5.6 grams of MG taken orally by a 70 kg human. The total alkaloid content in kratom leaves ranges from 0.5 to 1.5% (Hassan et al., 2013). Mitragynine makes up approximately 60% of this extract (Prozialeck et al., 2012; Philipp et al., 2010; Kapp et al., 2011). Based on this, 1 gram of kratom leaves would contain around 15 mg of alkaloids (based on the 1.5% figure), about 9 mg of which would be MG. This would suggest that a human would need to consume 630 grams of kratom leaves (or extract) to obtain a subjective effect that would fully substitute for morphine – the equivalent of over 500 2-ounce bottles commonly sold in stores. Although kratom leaves also contain smaller quantities of other alkaloids including 7-OH-MG, which is more potent at the mu opioid receptor, impractically large quantities of kratom would have to be consumed, even assuming some subjective effects of these other alkaloids.

As previously noted, generalization with an active substance known to cause dependence in itself is not necessarily indicative of dependence potential (Ator and Griffiths, 2003). The finding that MG substituted to the morphine discriminative stimulus when injected at very high dosages in rats supports the conclusion that the effects of kratom are mediated at least in part by opioid receptors; however, the relevance of these findings to human effects and consumption are limited.

3.1.1.2 Reinforcement

Centrally-acting drugs that produce highly pleasurable (rewarding) or psychologically reinforcing subjective effects in animals and man can lead to craving or addiction and also to diversion and nonmedical abuse, if the effect is strong enough. Many drugs that are powerful reinforcers in man are also reliably self-administered by various animal species (e.g., rats, dogs, monkeys or baboons; Ator and Griffiths, 2003).

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[3] Based on the calculated absolute oral bioavailability value of 3.03% (Parthasarathy et al., 2010)

There have been no studies of the reinforcing effects of kratom as an herbal product. However, as discussed below, there has been a study of the reinforcing value of a kratom extract, and studies have examined the reinforcing value of MG when given by injection to animals. The reinforcing value of the extract was less than that of MG. In studies of MG, doses of 5 mg/kg to 10 mg/kg, i.p. were shown to increase conditioned place preference (CPP) relative to placebo. As is the case with the discrimination study, the relevance of this to human consumption is not clear, having involved injections of extremely high doses, far beyond what could reasonably be consumed by a human from current products. Nonetheless, such research is important in helping to understand the mechanisms of action of kratom.

Sufka et al. (2014) also used the CPP model to characterize the psychoactive properties of *Mitragyna speciosa* MeOH extract (50, 100, 300 mg/kg, i.p.), *Mitragyna speciosa* alkaloid-enriched fraction (12.5, 25, 75 mg/kg, i.p.), and MG (5, 10, 30 mg/kg, i.p.) in rats. Rats were given eight counter-balanced drug versus vehicle conditioning trials followed by a preference test conducted under drug-free states. S(+)-amphetamine (1 mg/kg) served as the positive control and haloperidol (0.8, 1.0 mg/kg) served as the negative control in both studies. Rats showed place preference to MG that was similar to that of S(+)-amphetamine. This CPP effect was much less pronounced with the *Mitragyna speciosa* extract and its fraction. The preference scores for the 5 and 30 mg/kg MG groups, but not the 10 mg/kg group, were significantly higher than those for the vehicle.

Yusoff et al. (2016) examined the potential rewarding properties of injected MG using the CPP model. Rats that were conditioned with morphine (10 mg/kg, i.p.) and methamphetamine (1 mg/kg, i.p.) established a significant CPP for the drug-paired chamber. MG induced a significant CPP at doses of 10 mg/kg, i.p. and 30 mg/kg, i.p., but MG doses of 1 mg, i.p. and 5 mg, i.p. did not produce a significant effect.

Taken together, these studies suggest that an injected dose of 5 mg/kg was required to produce conditioned place preference in rats, which would equate to an oral dose of 165 mg/kg. Converting this to a human equivalent dose based on body surface area, this would equate to 26.6 mg/kg in humans, or over 1.8 grams of MG taken orally by a 70 kg human. The total alkaloid content in kratom leaves ranges from 0.5 to 1.5% (Hassan et al., 2013). Mitragynine makes up approximately 60% of this extract (Prozialeck et al., 2012; Philipp et al., 2010; Kapp et al., 2011). Based on this, 1 gram of kratom leaves would contain around 15 mg of alkaloids (based on the 1.5% figure), about 9 mg of which would be MG. This would suggest that a human would need to consume around 200 grams of kratom leaves (or extract) to obtain a reinforcing effect – over 150 2-ounce doses. Although kratom leaves also contain smaller quantities of other alkaloids including 7-OH-MG, which is more potent at the mu opioid receptor, impractically large quantities of kratom would have to be consumed even assuming some subjective effects of these other alkaloids.

3.1.1.3 Relevance of Doses to Humans, and Equivalencies with Other Unscheduled Drugs

In assessing the abuse potential of a particular product, it is important to consider the dose and route of administration. Reports of kratom consumption show that kratom is virtually exclusively consumed via the oral route, and it is likely that it would be very difficult to extract MG from the leaf or powder without extensive experience in chemistry and access to laboratory equipment. In contrast, the rodent research cited in the section above administered the drug via the i.p. route. Oral absorption of MG is slow, prolonged, and was incomplete, with a calculated absolute oral bioavailability value of 3.03% (Parthasarathy et al., 2010). The table below compares the number of units that would be required to achieve discrimination and reinforcement from several over-the-counter products that are currently not controlled.

Table 1. Number of units that would be required to achieve discrimination and reinforcement from several over-the-counter products.

Drug	Discriminable Dose	Reinforcing Dose	Dose in Common Products
Mitragynine	10 mg/kg, i.p. (Harun et al., 2015)	5 mg/kg, i.p. (Sufka et al., 2014)	Around 200 grams of kratom leaves (or extract) to obtain a reinforcing effect – over 150 2-ounce doses
Caffeine	(N=7)- Three subjects discriminated 56 mg, three discriminated 18 mg and one discriminated 10 mg (Griffiths et al., 1990)	At the two lowest doses (100 and 200 mg) 5 of the 12 subjects demonstrated significant caffeine positive reinforcement at one or both doses (Griffiths & Woodson, 1988)	Excedrin Extra Strength Caplets – 65 mg/caplet 10 Hour Energy Shot- 422 mg 5 Hour Energy- 200 mg Brewed coffee- 163 mg/8 oz Monster energy drink- 160 mg/16 oz Coca Cola- 34 mg/12 oz (http://www.caffeineinformer.com/the-caffeine-database)
Dextromethorphan	No human studies 30 mg/kg, i.p. in rats (Gavend et	Doses of 400 and 800 mg/70 kg increased drug liking scores. 92%	Robitussin Maximum Strength 10 mg//5 ml – 480 mg/8 oz bottle Mucinex DM Max Strength – 60 mg/tablet. 840 mg/14 count package

Drug	Discriminable Dose	Reinforcing Dose	Dose in Common Products
	al., 1995)	of subjects reported 400 mg/70 kg as feeling like they had received a “classic hallucinogen” (Reissig et al., 2012)	
Diphenhydramine	In rats, partial generalization to cocaine (78%) at 17.8 mg/kg (Gauvin, 1995)	400 mg increased end of day scores on liking and take drug again (Preston et al., 1992)	Sleep aid liquidcaps – 50 mg/cap, package of 32 (1600 mg total) Equate nighttime sleep aid – 25 mg-100 capsules per box (2500 mg)
Non-Alcoholic Beer	55% of subjects could be trained to discriminate 0.2 g/kg alcohol from placebo (Jackson et al., 2001)	Self-administration of ethanol at doses of 5-7 grams (Bigelow et al., 1977)	In the United States, one "standard" drink contains roughly 14 grams of pure alcohol, which is found in: • 12 ounces of regular beer, which is usually about 5% alcohol • 5 ounces of wine, which is typically about 12% alcohol • 1.5 ounces of distilled spirits, which is about 40% alcohol O’Douls- 0.4%- 1.12g
Nicotine	<1 mg by smoked, oral “chew”, or intravenous in humans	<1 mg by smoked, oral “chew”, or intravenous in humans (Henningfield et al., 2005; US DHHS, 2010)	All common tobacco products contain and deliver substantially higher doses but are typically used only as much as necessary to produce the desired effects. Former Surgeon General Koop, the first SG to conclude that nicotine met all criteria as an addictive drug, testified on behalf of allowing then prescription nicotine gum and patches to be

Drug	Discriminable Dose	Reinforcing Dose	Dose in Common Products
			approved for over the counter sales to make it more readily available for consumers to use as they desired to quit smoking.

It should also be noted that there are a variety of other herbal and consumer products that likely have some reinforcing effects, but are not controlled substances. For example, nutmeg contains myristicin, a natural compound that can produce hallucinogenic effects if taken in doses of around five teaspoons. When taking large amounts of nutmeg, it may take hours for auditory hallucinations to occur. This could result in increased overdose risk if the user thinks they haven't taken enough.

There are a variety of herbs and products with sedative effects, including the following:

- Chamomile
- Passionflower
- Ashwagandha
- Schisandra
- California Poppy
- Hops
- Kava
- Lavender
- Lemon Balm
- St. John's Wort
- Red Clover
- Catnip
- Valerian
- Motherwort
- Skullcap
- Poppy seeds
- Hemp seeds/oil

Herbs that are commonly used and sometimes abused for energy bursts include guarana and kola nut, both of which contain caffeine.

Poppy seeds are harvested from the opium poppy and contain a mixture of opium alkaloids (e.g., morphine, codeine, thebaine). Poppy seeds are used as foodstuffs in many parts of the world. Depending upon the seed source, harvesting practices, and washing procedures, the content of opium alkaloids in poppy seed is widely variable. A serving of poppy seeds (e.g., poppy seed bagel) may contain a few micrograms to a few milligrams of opium alkaloids. Some foodstuffs contain larger amounts of poppy seeds (strudel prepared with poppy seeds). Due to the variable alkaloid content in poppy seeds, it is not possible to estimate what a standard serving of poppy seeds contains in terms of morphine content, but according to reports, the content has been high enough to trigger workplace drug testing for some workers who consumed foods with poppy seeds (Thevis et al., 2003; Lachenmeier et al., 2010; Moeller et al., 2004; U.S. Anti Doping Agency, 2014).

Hemp seeds and oil are harvested from the cannabis plant and may contain tetrahydrocannabinol (THC), the psychoactive ingredient in cannabis material. Normally, the THC in these products are quite low, but some individuals have tested positive for THC metabolites following ingestion of these products, most notably, with hemp oil products. DEA regulation was recently instituted that exempted hemp oil containing any amount of THC from the CSA if the hemp oil was not used or intended for human consumption. 21 CFR 1308.35.

3.1.2 Summary of Factor 1

The findings above suggest that the main alkaloid in kratom, MG, provides some evidence of abuse potential when injected at extremely high dosages in animals. Specifically, the data suggest that MG shares some discriminative stimulus effects with morphine in rats when injected at very high doses, and that the substance produces reinforcing effects. However, as noted elsewhere in this report, it would be extremely difficult to isolate the MG from kratom leaves to make an injectable preparation of MG. Further, the amount of MG in kratom leaves is only about 9 mg per gram, and the oral bioavailability of MG is quite low (3.03%). This would suggest that huge quantities of kratom would need to be consumed to obtain the effects seen after taking a pure mu opioid such as morphine. Thus, although important as basic research, the relevance to human oral consumption is limited. Furthermore, in contrast to the effects of increasing the dose of substances of high abuse potential (e.g., prototypic opioids, stimulants, and sedatives), increasing the dose of kratom is more likely to produce undesirable gastrointestinal effects, constipation, and lethargy, and little additional mood enhancement.[4]

In addition, as discussed in this section and elsewhere in this report, it appears that the vast majority of kratom consumption is for perceived benefits and social/occupational enhancement, and not for the euphoric effects of the product.

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[4] These observations are limited by the absence of classic human abuse potential studies, such as the ones in which the authors of this report are expert (e.g., FDA, 2010; Schuster and Henningfield, 2003), but are consistent with clinical, ethnographic, and internet reports, as well as the pharmacology as known to date and discussed further on this this report (Raffa, 2015; Henningfield, 2015; Ward et al., 2011; Warner et al., 2016).

3.2 Factor 2: Scientific evidence of its pharmacological effect, if known

The pharmacology of kratom was reviewed recently by Warner et al. (2016) and some of this discussion was drawn from that review as well as Henningfield (2015). Over 40 different constituents have been isolated from kratom (EMCDDA, 2015; Gogineni et al., 2014), and kratom leaves have been found to contain over 25 alkaloids (Tanguay, 2011; Hassan et al., 2013). The alkaloids MG and 7-OH-MG are believed to be the primary active alkaloids in the plant (Tanguay, 2011; Warner, 2016). The total alkaloid content in kratom leaves ranges from 0.5 to 1.5% (Hassan et al., 2013). Mitragynine makes up approximately 60% of this extract with 7-OH-MG accounting for only up to 2% (Prozialeck et al., 2012; Philipp et al., 2010; Kapp et al., 2011). In a recent study by Kruegel et al. (2016), the authors found only trace quantities of 7-OH-MG (by mass spectrometry) in their extractions of the raw plant material, and concluded that it is doubtful that 7-OH-MG is a universal constituent of all Mitragyna speciosa preparations and is unlikely to generally account for the psychoactive properties of this plant.

Mitragynine is an indole-containing alkaloid, structurally similar to yohimbine, a component of the common dietary supplement yohimbe (Hassan et al., 2013; Prozialeck et al., 2012; Rosenbaum et al., 2012). Both mitragynine and 7-OH exhibit nanomolar binding affinities for the μ-opioid receptors and possess functional activity in tissue assays (Takayama et al., 2002; Matsumoto et al., 2004). In addition, the antinociceptive effects of mitragynine and 7-OH-MG in several rodent models are also inhibited by naloxone (Takayama et al., 2002; Matsumoto et al., 2004; Matsumoto et al., 1996). However, mitragynine was found to produce markedly less respiratory depression than codeine (Macko et al., 1972).

In animal models, mitragynine exhibits activity on supraspinal μ- and δ-opioid receptors causing its characteristic analgesic effects (Rosenbaum et al., 2012; Hassan et al., 2013; EMCDDA, 2015; Prozialeck, 2012). With consideration to the interactions at the cellular level, studies suggest that neurotransmitter release from the nerve endings at the vas deferens is inhibited (Prozialeck, 2012). This inhibition is suggested to occur through the obstruction of neuronal calcium (Ca2+) channels (Hassan et al., 2013; Philipp, 2010). Blocked stimulation of serotonergic 5-HT2A receptors and stimulation of postsynaptic alpha-2 adrenergic receptors are thought to contribute to stimulant activity (Rosenbaum et al., 2012; EMCDDA, 2015).

In animal models, additional psychoactivity is said to exist as a consequence of binding affinities exceeding that of morphine at the δ- and κ- opioid central receptors (Prozialeck, 2012). Moreover, 7-OH-MG provides high opioid receptor affinity with agonist properties (EMCDDA, 2015; Prozialeck, 2012). While polarity is increased due to the additional hydroxyl group on 7-OH-MG as compared to mitragynine, increased activity of 7-OH-MG is otherwise not well understood (Prozialeck, 2012).

Unlike the preclinical models, Kruegel et al. (2016) showed that at the human opioid receptors (human μ-, δ-, and κ-opioid receptors), mitragynine acted as a partial agonist at human μ-opioid receptors (EC_{50} = 339 ± 178 nM; maximal efficacy (E_{max}) = 34%). In contrast, at human κ-opioid receptors, mitragynine was a competitive antagonist (IC_{50} = 8.5 ± 7.6 μM; pA_2 = 1.4 ± 0.40 μM), fully inhibiting the activity of the reference agonist U-50,488. Similarly, mitragynine acted as an antagonist at human δ-opioid receptors, but with very low potency. The other major natural alkaloids paynantheine, speciogynine, and speciociliatine, showed no measurable agonist activity at any of the human opioid receptors at concentrations up to 100 μM, and only weak antagonist effects were observed. This partial agonist activity is consistent with the observation that mitragynine was found to produce markedly less respiratory depression than codeine (Macko et al., 1972), as well as the lack of respiratory depression-related deaths discussed elsewhere in this report.

7-OH-MG was also characterized and found to be a potent, partial agonist at human μ-opioid receptors (EC_{50} = 34.5 ± 4.5 nM; E_{max} = 47%). Further, it acted as a competitive antagonist at both human κ-opioid receptors (IC_{50} = 7.9 ± 3.7 μM; pA_2 = 490 ± 131 nM) and human δ-opioid receptors (IC_{50} > 10 μM). The partial agonist activity of mitragynine and 7-OH-MG at the human receptors was further confirmed in antagonist experiments, as both compounds were able to partially inhibit the response elicited by the full agonist [D-Ala$_2$, N-Me-Phe$_4$, Gly-ol$_5$]-enkephalin (DAMGO). As with MG, the partial agonist activity of 7-OH-MG is consistent with the lack of respiratory depression-related deaths discussed elsewhere in this report.

Although MG (Warner et al., 2016; Hassan et al., 2013) and sometimes 7-OH-MG (Matsumoto et al., 2005) have been reported as 13 times more potent than morphine, many of the references to support this figure appear to not actually report this finding. In fact, a wide range of findings have been reported for MG and 7-OH-MG related to relative potency (the amount needed to produce an effect) and strength (the maximal effect, e.g. guinea pig ileum muscle twitch, or analgesic effect on mice placed on an uncomfortably but not burning hot plate). These are often reported in article abstracts and in turn by the media as "morphine" or "opioid" like effects with little context for what was actually studied, what was found, and its relevance or lack thereof to human use and effects.

For example, Warner et al. (2016) cites Rosenbaum et al. (2012) to support the statement that MG has "approximately 13 times the potency of morphine in regards to its opioid-like effects". In turn, Rosenbaum et al. (2012) cite Vicknasingam (2010) and Matsumoto et al. (2005). Vicknasingam (2010) states "Two alkaloids in kratom—mitragynine and alkaloid 7-hydroxymitragynine—act as agonists to supraspina mu- and delta-opioid receptors and produce effects similar to morphine. In fact, the latter [i.e., 7-OH-MG] exhibited about 13 times higher potency than morphine…." Matsumoto's only discussion of the 13-times figure says "7-hydroxymitragynine inhibited electrically induced contraction through the opioid receptors, and its effect was about 13-fold more potent than morphine." Thus it appears that 7-OH-MG (not MG) may exhibit effects 13 times greater than morphine on some effects, but the relative potency of MG appears less than that of morphine. For example, Watanabe et al (1997) states "Mitragynine was 10 fold less potent than morphine." It is also reported to be 5-fold weaker than morphine in analgesiometic tests in mice and had a potency ratio of inhibitory effect on ileum contraction that was 6-fold less potent than that of morphine (Watanabe et al., 1997). Taken together these studies confirm that these molecules, which the investigators note are structurally distinct from opioids, do produce some opioid like effects. Furthermore, their relative potency and strength are far from fully characterized in laboratory models and is need of further research. Research is also need to assess the generality of such laboratory findings to human use and effect.

It should be noted that potency is often improperly equated with strength with respect to abuse potential and toxicity when all it really means is the relative quantity of a substance that is required to produce a specific effect, and not the strength of the effect. Thus, for example, nicotine appears to be at least 5-10 times more potent than cocaine in producing certain cocaine-like effects in animals and humans, including reinforcement (Goldberg et al., 1983). However, pure nicotine, despite its ready over the counter and commercial availability over most of the 20th century and presently, has never emerged as a substance of abuse or a public health threat in its own right. This is consistent with the fact that the strength of nicotine as a euphoriant and the generality of conditions in which it serves as a strong reinforcer is less than for cocaine (Goldberg et al., 1983; Henningfield & Goldberg, 1985; Henningfield et al., 2016). Moreover, despite tens of millions of users of nicotine and everyday exposures to nicotine-containing products by children and infants in the US, and many reports to poison control centers and emergency departments, there have been only a few deaths in children or adults that were attributed primarily to nicotine. For example, between January 2012 and April 2015, there was only one death associated with a nicotine or tobacco product among children under 6 years reported to the National Poison Data System (Kamboj et al., 2016).

Taken together, although progress has been made in understanding the pharmacology of kratom and MG and 7-OH-MG in particular, more research is needed to fully characterize the mechanisms of action that contribute to a novel profile of some opioid-like and stimulant-like effects that may be important in the consumption of kratom products. In the absence of clarity about the pharmacological mode of action, observed effects are the most reliable guide to the impact of kratom.

3.3 Factor 3: The state of current scientific knowledge regarding the drug or other substance

Kratom leaves and crushed or powdered leaves are readily available on the internet and in stores in most states, but this material is not reported to be used by nasal insufflation, smoking, or intravenously (in contrast to opioids and stimulants that are commonly used by such diverse routes to speed absorption and intensify their effects). In addition to the apparently low potential to produce strong effects sought by persons who abuse drugs, the physical nature of the leaf material with its high ratio of cellulose fiber likely deters use by such routes because large amounts of material would need to be placed in the nose or smoked to produce effects. By analogy, caffeinated products are also not reportedly used by injection, smoking, or snorting likely in part because of relatively low potential to produce strong euphoriant effects as compared to cocaine (Garrett and Griffiths, 2001).

It would not likely be simple or inexpensive to extract and concentrate the MG or 7-OH-MG from kratom leaves, and it would require sophisticated equipment and chemistry training, but it would be theoretically possible. In Southeast Asia where the raw material is plentiful and there are many clandestine laboratories for synthesizing substances for abuse, kratom-derived products have not been a target, likely due to the apparently low abuse liability of mitragynine and limited euphoriant-like effects produced by the product. Furthermore, in contrast to the effects of increasing the dose of substances of high abuse potential (e.g., prototypic opioids, stimulants and sedatives), increasing the dose of kratom is more likely to produce undesirable gastrointestinal effects, constipation, and lethargy, and little additional mood enhancement.

In rodents, the analgesic effects of mitragynine have been evaluated in hot plate and tail-pinch tests. Administration of mitragynine (35 mg/kg) increased the pain threshold in hot plate tests, and its effects were inhibited by naloxone (1 mg/kg, i.p.) (Shamima et al., 2012). 7-OH-MG has also been reported to produce analgesia when evaluated in in vivo pharmacological studies. For example, Matsumoto et al. (2006) reported that when 7-OH-MG was administered subcutaneously (s.c.) in mice, there was an increase in the pain threshold for both the tail-flick (ED50 = 0.80 mg/kg, s.c.) and hot plate (ED50 = 0.93 mg/kg, s.c.) tests, and its effects were inhibited by naloxone. Comparatively, the ED50 of morphine (s.c.) in tail-flick and hot-plate tests are 4.57 mg/kg and 4.08 mg/kg, respectively (Matsumoto et al., 2006; Matsumoto and Horie, 2014).

The pharmacodynamic effects of kratom have been summarized in reviews (see Warner et al., 2016; Prozialeck, 2012). Kratom users can expect to experience full effects in about 30–60 min after ingestion, although onset can be noticeable within about 10–20 min. The half-lives of mitragynine and 7-OH-MG are about 3.5 and 2.5 h, respectively. Both are eliminated from the body primarily with the urine (Prozialeck, 2012; Neerman et al., 2013). The pharmacokinetics following oral administration of mitragynine in humans has been proposed as a two-compartment model based on the observed kinetics in ten healthy human male volunteers (Trakulsrichai et al., 2015). Certain conditions such as prior food consumption or taking kratom in capsule form can delay the initial response. The effects of kratom typically last about 5–7 h, with the strongest effects at about 2–4 h after ingestion, although weak aftereffects can be felt as late as the next day (Rosenbaum et al., 2012; Prozialeck, 2012; Scott et al., 2014; Maruyama et al., 2009). Current pharmacokinetic data in both animals and humans is limited, and there appears to be a significant variability within each species and differences between species in terms of mitragynine pharmacokinetics.

Approximately 1–5 g of raw leaves, which is defined as a low to moderate dose, will yield mild stimulant effects (EMCDDA, 2015; Prozialeck, 2012). The onset of effects begins to be experienced about 10 min or more after using a few grams of dried leaves (EMCDDA, 2015). This dosage amount is often related to the stimulant effects commonly used by labor workers in Southeast Asia to fight fatigue (Prozialeck, 2012). Not only has increased work capacity been reported by users, but alertness, sociability, and increased sexual desire are said to occur (EMCDDA, 2015). At this dose, the user may also possess normal to slightly contracted pupils and blushing. Unwanted side effects are generally minimal; however, anxiety and internal agitation have been described (Prozialeck, 2012).

Using from 5 to 15 g of kratom leaves may provide the user with pain and opioid withdrawal symptom relief (EMCDDA, 2015; Prozialeck, 2012). Both mitragynine and 7-OH-MG yield analgesic and antinociceptive effects. Euphoria is more often achieved at this higher level, but these effects tend to be less intense as compared with opioid drugs (Prozialeck, 2012).

When exceeding 15 g of kratom leaves, one would expect to experience stupor, mimicking the effects associated with opioids (EMCDDA, 2015; Prozialeck, 2012). Initially, sweating, dizziness, nausea, and dysphoria will often result. These effects quickly subside and are followed by calmness and a dreamlike state (EMCDDA, 2015).

Frequent users of kratom, primarily in Southeast Asia, have displayed instances of the atypical symptoms tremor, anorexia, weight loss, seizures, and psychosis (Hassan et al., 2013; Prozialeck, 2012). Such individuals are likely using high doses of kratom for a prolonged period of time (Hassan et al., 2013; Prozialeck, 2012). The relevance of these potential effects from a public health perspective appears low as suggested in the analysis of Factor 5 and 6; however, research on this issue should be continued and extended.

This analysis is consistent with the conclusions of other recent reviews of the state of kratom science, which reveal a novel substance in need of further research to better understand its mechanisms of action as well as effects, particularly in dosage forms relevant to oral consumption by humans.

3.4 Factor 4: Its history and current pattern of abuse

3.4.1 History

The history of kratom presence and consumption in the US is recent, compared to Southeast Asia, and not well documented. Anecdotal reports, e.g., by Hmong immigrants in the 1980s and 1990, suggest that the Hmong and other immigrants from the Southeast Asia region likely brought kratom consumption practices to the US, and discussions with some have suggested availability in some Asian food product stores for many years (JEH discussions with Hmong community members in Minnesota). However, there has been little documentation of this in the literature other than anecdotal reports (see an anecdote reported in Axelrod and Windell, 2012, p.56). Broader commercial marketing of kratom products in the US by internet and in various health and natural food stores apparently began to increase in the early 2000s. A kratom industry survey estimated that by 2016, there were approximately 10,000 vendors selling kratom products in the US (Botanical Education Alliance, 2016).

Frequency of consumption of kratom, whether by consumption of home brewed liquids or commercial products, appears largely determined by individual preferences and reasons for consumption. For example, United Naturals reported that its average customer purchased and/or reported approximately 2-3 2oz (i.e., two “dose”) bottles per week, whereas other consumers make their own tea-like preparations on a daily basis. See the Appended testimonials collected by the American Kratom Association, which include descriptions of a range of patterns from daily to a few times per week to fit the needs and desires of the respondents. None of the users described consuming massive amounts of tea or hundreds of bottles in a single setting, as would apparently be required to produce the effects seen in the rodent studies described above.

Typical mode of kratom consumption

The most common mode of consumption in the US is in the form of liquids that are either prepared by consumers or purchased as manufactured products, often in small, 2 ounce containers as have become increasingly popular for caffeinated energy based “shot” drinks and other supplements. Consumers who prepare their own liquids use both hot and cold water extraction methods similar to making tea or coffee. Leaf material, which may be whole leaf but more commonly chopped or powdered, can be steeped or boiled, or cold water extracted. Lemon juice or other acids may be added to facilitate extraction. Sugar, honey, and other sweeteners and flavoring ingredients are often added to mask the generally perceived unpleasant and bitter taste of the liquids. A public health benefit of the general distasteful nature of the liquids is probably the discouragement of consumption by children. In fact, given the millions of preparations made in homes and sold by 10,000 vendors throughout the US, this may help contribute to apparently infrequent inadvertent consumption by children and reporting to emergency departments and poison centers in addition to the apparent intrinsic low acute toxicity of the mitragynines as discussed further on.

In Southeast Asia, leaf chewing is common as would be expected given the ready access to trees or inexpensive marketed harvested leaves. There have been some reports of leaf smoking in Southeast Asia but this does not appear common in Southeast Asia where product is readily available or in the US. This is in striking contrast to opioids which are rarely consumed as beverages or in foods and for which the preferred routes of use are smoking, injecting, and by nasal insufflation (“snorting”). There is a striking parallel in fact with respect to the stimulant caffeine, which is almost exclusively consumed in the form of beverages, also used in many foods, but rarely consumed by routes that are typical of other stimulants such as cocaine and amphetamine which are often used by smoking, injecting, and by nasal insufflation. For further comparison, the kratom tree and the coffee tree are both tropical, deciduous, evergreens in the coffee family (Rubiaceae) native to Southeast Asia.

3.4.2 Federal Surveys

Monitoring the Future Survey (MTF) and Treatment Episodes Datasets (TEDS)

Among federal surveys, the youth and young adult targeted MTF survey and the TEDS were evaluated. MTF data are available through 2015 and TEDS through 2013. Neither of these surveys have reported kratom consumption or treatment seeking for kratom dependence, respectively. That does not mean there has been no abuse or kratom dependence treatment seeking; however, it does reflect the absence of signals and the lack of recommendations from affiliate researchers and treatment clinics that kratom abuse or dependence treatment should be added to the surveys at this time. Those systems, like most other such drug use and abuse-related surveillance systems, are designed and implemented so as to capture the emergence in trends of use, abuse and treatment needs. There may be a few years' lag time unless such problems are emerging rapidly and/or are considered public health priorities; however, given that kratom has been used in the US for decades, one would predict that, if kratom were emerging as a public health or abuse problem, it would have been evident from these surveys.

National Survey on Drug Use and Health (NSDUH)

The NSDUH is generally considered to be a sensitive indicator of emerging trends in substance abuse, including adoption of new substances, and it includes collection of self-reported new and novel products and substances by its open-ended questions. Thus, although it does not yet include kratom/mitragynine-specific questions, since 2010 through the most recently published data release that covered 2014, there were a total of two (2) kratom mentions (unweighted – not nationally representative). By contrast, and over the same time frame, mentions of oxycodone, heroin, cocaine, amphetamine, marijuana, and other prototypic substances of abuse were in the many thousands. Aspirin mentions ranged from 17 to 22 per year, while diphenhydramine mentions ranged from 12 to 29 per year. See Table 2.

Table 2. Number of Unweighted Cases of Kratom, Aspirin, Diphenhydramine, and Other Substances Reported to the National Survey on Drug Use and Health, 2010-2014.

	NSDUH – Number of Unweighted Cases				
	2010	*2011*	*2012*	*2013*	*2014*
Kratom/Mitragynine†	1	0	0	0	1
Oxycodone§	2,068	2,097	2,017	1,877	1,835
Heroin§	771	826	829	842	946
Cocaine§	6,464	6,260	6,009	5,653	6,636
Amphetamine§	3,916	4,136	4,113	4,171	4,179
Marijuana§	22,842	22,994	22,238	22,163	23,462
Aspirin (acetylsalicylic acid) †	3	5	9	7	3
Diphenhydramine†	37	36	23	28	16

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† unweighted non-medical use case mentions from open-ended response items only

§ unweighted non-medical use case mentions from drug-specific and open-ended response items

3.4.3 Other Federal Data Sources

Drug Abuse Warning Network (DAWN)

There have been no reports of kratom or mitragynines in the DAWN system; however, since DAWN monitoring ended as of December 31, 2011, all that can be concluded is that DAWN-detected signals were not occurring before 2012. It is telling, however, that when clearly high risk products such as fentanyl emerged even in small geographic areas, DAWN quickly picked up associated problems. Kratom likely had at least a decade of widespread use without generating any reports in the DAWN system.

National Forensic Laboratory Information System (NFLIS)

The NFLIS is a monitoring system of the Diversion Control Division of the DEA. It systematically collects and reports findings from drug chemistry analyses from law enforcement seizures (see https://www.deadiversion.usdoj.gov/nflis/). The materials collected in seizures (e.g., during "drug busts" and drug dealer arrest operations) are analyzed by more than 300 state and local forensic laboratories nationwide. It thus provides a means of geographic tracking of what sorts of substances are being recovered, including diverted legally manufactured drugs, illicitly manufactured products (e.g., heroin and crack cocaine), and other substances and products.

Nearly two million analyses of drugs and other substances are tested annually. These include findings on opioids, depressants and tranquilizers, hallucinogens, anabolic steroids, and stimulants. These assessments thus provide statistically representative national and regional drug item estimates for the likelihood that a given substance will be found together with the most frequently identified drugs, and thereby some sense of the mix of substances that have been collected in seizure operations. These reports are measures of seizures, not measures of actual use, abuse, adverse reactions, or overdose deaths.

Mitragynine was first reported in the NFLIS system in 2010. From 2013 to 2015, mitragynine reports accounted for approximately 0.01% of total reports. Specifically, 181 mitragynine reports were recorded in 2013 (out of 1,540,647 total reports), 137 in 2014 (out of 1,511,313 total reports), and 129 in 2015 (out of 1,549,466 total reports). The fact that these identifications were a new category, albeit at very low rates, led the DEA to place mitragynine on its "watch list," meaning essentially that laboratories and investigators are encouraged to be alert for products potentially containing mitragynine and to be testing for mitragynine.

To provide some perspective of how mitragynine reports compare to opioids, Table 1 from the NFLIS July, 2015 special report on "Opiates and Related Drugs Reported in NFLIS, 2009-2014 (NFLIS, July, 2015)[5] is shown below (See Table 3). Among these substances, heroin accounted for 699,847 (48.64%), followed by oxycodone at 285,381 (19.83%), and hydrocodone at 235,417 (16.36%), together accounting for approximately 85% of the 1,438,933 reports. Mitragynine reports totaled 42 (0.03%) in the second six months of 2011 and 88 (0.06%) in the first six months of 2014, and totaled 458 (0.03% overall) through June, 2014.

As confirmed by NFLIS, kratom is available to persons who have been found with substances of abuse, yet kratom has not emerged as a substance of abuse by any of the federal surveillance systems. This is not the profile of a substance with intrinsic activity indicative of a high risk of abuse, dependence, or addiction. It is more the profile of any number of substances including caffeinated products and over the counter medicines that are consumed and used by many people for the benefits that they provide, regardless of whether those individuals use, abuse, or distribute substances of abuse.

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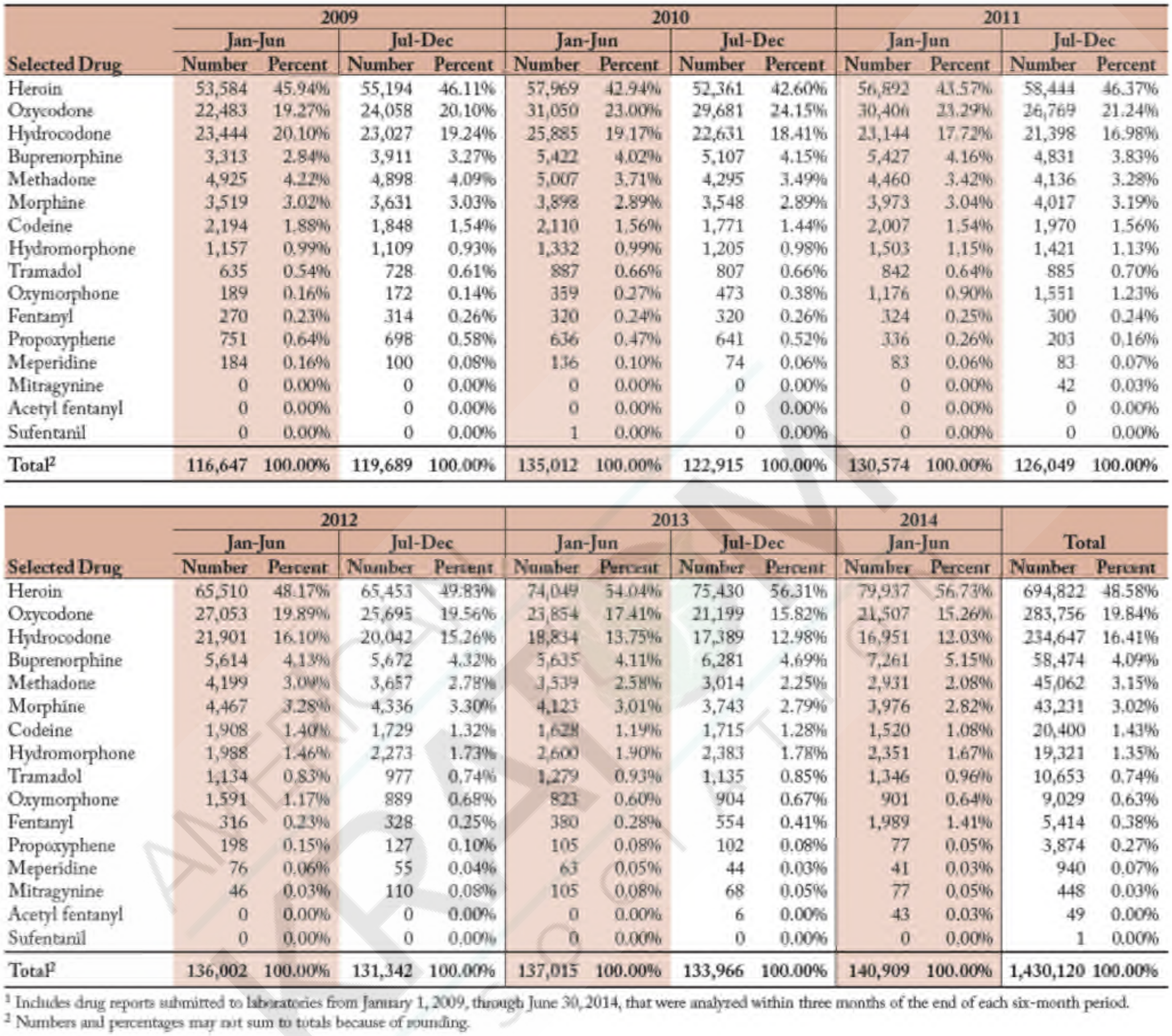
[5] https://www.deadiversion.usdoj.gov/nflis/spec_rpt_opioids_2014.pdf.

Table 3. National Semiannual Estimates of Selected Opiate and Related Drug Reports in NFLIS, 2009-2014.



	2009				2010				2011			
	Jan-Jun		Jul-Dec		Jan-Jun		Jul-Dec		Jan-Jun		Jul-Dec	
Selected Drug	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Heroin	53,584	45.94%	55,194	46.11%	57,969	42.94%	52,361	42.60%	56,892	43.57%	58,444	46.37%
Oxycodone	22,483	19.27%	24,058	20.10%	31,050	23.00%	29,681	24.15%	30,406	23.29%	26,769	21.24%
Hydrocodone	23,444	20.10%	23,027	19.24%	25,885	19.17%	22,631	18.41%	23,144	17.72%	21,398	16.98%
Buprenorphine	3,313	2.84%	3,911	3.27%	5,422	4.02%	5,107	4.15%	5,427	4.16%	4,831	3.83%
Methadone	4,925	4.22%	4,898	4.09%	5,007	3.71%	4,295	3.49%	4,460	3.42%	4,136	3.28%
Morphine	3,519	3.02%	3,631	3.03%	3,898	2.89%	3,548	2.89%	3,973	3.04%	4,017	3.19%
Codeine	2,194	1.88%	1,848	1.54%	2,110	1.56%	1,771	1.44%	2,007	1.54%	1,970	1.56%
Hydromorphone	1,157	0.99%	1,109	0.93%	1,332	0.99%	1,205	0.98%	1,503	1.15%	1,421	1.13%
Tramadol	635	0.54%	728	0.61%	887	0.66%	807	0.66%	842	0.64%	885	0.70%
Oxymorphone	189	0.16%	172	0.14%	359	0.27%	473	0.38%	1,176	0.90%	1,551	1.23%
Fentanyl	270	0.23%	314	0.26%	320	0.24%	320	0.26%	324	0.25%	300	0.24%
Propoxyphene	751	0.64%	698	0.58%	636	0.47%	641	0.52%	336	0.26%	203	0.16%
Meperidine	184	0.16%	100	0.08%	136	0.10%	74	0.06%	83	0.06%	83	0.07%
Mitragynine	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	42	0.03%
Acetyl fentanyl	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Sufentanil	0	0.00%	0	0.00%	1	0.00%	0	0.00%	0	0.00%	0	0.00%
Total[2]	116,647	100.00%	119,689	100.00%	135,012	100.00%	122,915	100.00%	130,574	100.00%	126,049	100.00%

	2012				2013				2014		Total	
	Jan-Jun		Jul-Dec		Jan-Jun		Jul-Dec		Jan-Jun			
Selected Drug	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Heroin	65,510	48.17%	65,453	49.83%	74,049	54.04%	75,430	56.31%	79,937	56.73%	694,822	48.58%
Oxycodone	27,053	19.89%	25,695	19.56%	23,854	17.41%	21,199	15.82%	21,507	15.26%	283,756	19.84%
Hydrocodone	21,901	16.10%	20,042	15.26%	18,834	13.75%	17,389	12.98%	16,951	12.03%	234,647	16.41%
Buprenorphine	5,614	4.13%	5,672	4.32%	5,635	4.11%	6,281	4.69%	7,261	5.15%	58,474	4.09%
Methadone	4,199	3.09%	3,657	2.78%	3,539	2.58%	3,014	2.25%	2,931	2.08%	45,062	3.15%
Morphine	4,467	3.28%	4,336	3.30%	4,123	3.01%	3,743	2.79%	3,976	2.82%	43,231	3.02%
Codeine	1,908	1.40%	1,729	1.32%	1,628	1.19%	1,715	1.28%	1,520	1.08%	20,400	1.43%
Hydromorphone	1,988	1.46%	2,273	1.73%	2,600	1.90%	2,383	1.78%	2,351	1.67%	19,321	1.35%
Tramadol	1,134	0.83%	977	0.74%	1,279	0.93%	1,135	0.85%	1,346	0.96%	10,653	0.74%
Oxymorphone	1,591	1.17%	889	0.68%	823	0.60%	904	0.67%	901	0.64%	9,029	0.63%
Fentanyl	316	0.23%	328	0.25%	380	0.28%	554	0.41%	1,989	1.41%	5,414	0.38%
Propoxyphene	198	0.15%	127	0.10%	105	0.08%	102	0.08%	77	0.05%	3,874	0.27%
Meperidine	76	0.06%	55	0.04%	63	0.05%	44	0.03%	41	0.03%	940	0.07%
Mitragynine	46	0.03%	110	0.08%	105	0.08%	68	0.05%	77	0.05%	448	0.03%
Acetyl fentanyl	0	0.00%	0	0.00%	0	0.00%	6	0.00%	43	0.03%	49	0.00%
Sufentanil	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	0.00%
Total[2]	136,002	100.00%	131,342	100.00%	137,015	100.00%	133,966	100.00%	140,909	100.00%	1,430,120	100.00%

[1] Includes drug reports submitted to laboratories from January 1, 2009, through June 30, 2014, that were analyzed within three months of the end of each six-month period.

[2] Numbers and percentages may not sum to totals because of rounding.

3.5 Factor 5: The scope, duration, and significance of abuse

As discussed in Factor 4 above, there appears to be little, if any, abuse of kratom in the US. To the extent to which benefits are provided by consumption of kratom-derived products, these appear possible with remarkably low risks of serious adverse effects as compared to opioids and there is little evidence or apparent risk that kratom products are used by routes other than oral beverage or food consumption, even though it is certainly theoretically possible to smoke, snort, or inject kratom extracts.

3.5.1 Internet monitoring

The dramatic growth of the Internet in the past 20 years has substantially changed the dissemination of ideas, contributed to trends in product use and misuse, and added new means of monitoring emerging substances. There are many websites that focus specifically on drug misuse and abuse, some intended to discourage such use as well as those that appear dedicated to providing information in support of, if not to encourage, misuse and abuse of drugs. An important limitation of the data is that they do not necessarily relate to incidence, prevalence, or to increases or decreases in population trends. For example, a single provocative posting might precipitate a series of postings (known as a “thread”) thereby creating a “bump” in the number of postings on a given topic which may not necessarily be related to population trends. Also, as is apparent by even a casual review of such websites, they including postings that can strain credulity. Thus, teams such as our group at PinneyAssociates led by Dr. Edward Cone, and the FDA’s Controlled Substances Staff, have learned to be careful in relying on such information for more than qualitative insights concerning the diversity of opinion and responses related to substances. Nonetheless, such insights, when compared against known pharmacology and epidemiology, can be useful in guiding policy including risk management efforts.

With the foregoing caveats in mind, and understanding that PinneyAssociates has not conducted an extensive evaluation of internet postings, the following provides representative examples of serious substance abusing persons who appear to have made efforts to compare kratom to their preferred substances.

Taken together, most of the postings involve what appear to be extremely high dosages of kratom substances and extracts, and self-made extracts from a variety of kratom sources: for example, users may combine several grams of kratom powder, several ounces of kratom leaves, and indeterminate forms of this or other substances. Some people have reported experiencing intoxication, euphoria, and other effects at these very high dosages, though typically, their comparisons to other drugs provide a basis for understanding why kratom and kratom products apparently are rarely the substance of choice among people who seek abused drugs and are in search of better ways to get better highs and euphoria. There are self-reports of dependence and withdrawal, but these tended to involve extremely high intakes of kratom, apparently along with other substances.

Table 4 provides what PinneyAssociates’ experience offers as a reasonable representation of kratom experiences.

Table 4. Verbatim accounts from Internet reports from a website that typically attracts people with histories of diverse substance use and abuse to describe their experiences

http://www.bluelight.org/vb/threads/398307-Kratom-experiences.

27-09-2008 03:28: *Here's my personal opinion, others have had better experiences: Kratom offers a pleasing buzz, but it only lasts about an hour. Then it's gone and I can't redose for another 12 or so hours. It just won't work again if I try to dose sooner. When I use it every day, the buzz gets less and less until it's practically worthless. Kratom just didn't do me very well. I hope you have a better experience with it.*

27-09-2008 04:28: *Kratom is somewhat self limiting when it comes to abuse, or daily recreational use, yes. Each day you use it, it becomes a bit less warm and less euphoric. But its pain relieving properties continue after those effects fade. Even after continued daily use there will always be noticeable anxiety relieving, and pain relieving properties. You can avoid losing some of the glow and euphoria by switching to different strains every so often.*

27-09-2008 08:15: *After LOVING oxy to death and losing my source, I sought out some Kratom to act as a substitute. If you're expecting something amazing, you will definitely be disappointed. It DOES feel like an opiate, kind of, but it's very very limited. I tried several strains in several different dosages, and yeah, it doesn't have that much to offer. Doing too much is awful - I felt nauseous for DAYS. Doing too little is just boring. There IS somewhat of a sweet spot but it just doesn't scratch where I itch, compared to oxy (and I never did that much oxy that frequently, and I hadn't in weeks before kratom, and so it's not just an addiction thing).*

28-09-2008 05:49: *Personally I like the taste of pod tea, the stronger the better. It's preferable to the odd taste of kratom (even though I will drink kratom tea straight as well). But Kratom has a numbing sensation on my mouth when I drink it, like pins and needles on the tongue. I've never really felt too much from kratom. I've had the so-called 10x extracts and the leaves, with the extracts I'd just down them with alot of water, and with the leaves just make some tea. I'd say that the effects were a bit stronger from the leaves, however. I had to use about 1/4 an ounce, which (if I remember correctly) was a few cups of tea...a french press would probably be even more effective, though. Subjectively the effects felt similar to a moderate dose of tramadol...especially the serotinergic wakefulness type of feeling. It was great for staving off withdrawals, but I couldn't see it being my drug of choice. After a certain point taking more kratom doesn't seem to increase or prolong the euphoria much. I'm willing to bet though that people who have never been addicted to opiates would enjoy this drug much more than those who are or have been.*

28-09-2008 06:00: "*Yes the taste of Kratom tea is disgusting. Thats why tea is no-longer the preferred method of ingestion by Kratom users. We use TNW= puddle on tongue, plop kratom in, swallow, follow with water. You wont feel too much from kratom. Its very subtle for most. The extracts are usually unbalanced and stimulative, rather than relaxing and euphoric. You took far too many leaves. I did the same thing when I first tried Kratom. You only need 2-3 tea spoons. Taking too much will make you sick, or could even ruin the effects all together. I guess you can't really take it and then just* *forget you took it. You need to recognize the effects and focus on them to feel nice. And yes, Re-dosing Kratom is useless, you will feel nothing more. It may make the aroma last longer, but it wont increase the potency of the smell."*

Similarly, Swogger et al. (2015) conducted a qualitative analysis of first-hand descriptions of human kratom consumption that were submitted to, and published by, a psychoactive substance information website (Erowid.org) as "experience reports." For such participation in the Erowid system people are asked to self-administer the substance, often at high dosage levels, and then report their effects over the next 8 hours. A caveat, based on the experience of the authors of this report, is that Erowid site participants would seem more likely than people in the general population to be heavy users and poly drug users and abusers, including many in this survey with self-reported use and dependence to prototypic opioids, cocaine, and other drugs.

Four general themes emerged as associated with kratom product consumption (see Swogger et al., 2015 for greater detail):

1. Positive experiences was the most prominent theme with euphoria occurring in 30.4% of the respondents especially at high dosages, relaxation in 23.6%, and increased energy in 8.7%.

2. Negative experiences including nausea, stomachache, and cramping occurred in 16.1%. This included alternating chills and sweats in 9.3%, dizziness and unsteadiness in 6.8%, and vomiting in 3.1%.

3. Neutral experiences occurred in about 10% of the respondents, which included numbness of the throat and mouth, visual alterations, and sedation.

4. Substitution occurred in 10.6%, meaning that 10.6% used kratom as a substitute for an unwanted substance. This included 9.9% who used kratom to relieve symptoms of withdrawal from another substance.

Themes that emerged from these experience reports indicate that kratom may be useful for analgesia, mood elevation, and anxiety reduction, and may aid opioid withdrawal management. Negative response themes also emerged, indicating potential problems and unfavorable "side" effects, especially stomach upset and vomiting.

A number (10.6%) of individuals reported successfully using kratom as a substitute to help abstain from the use of other substances perceived as addictive and/or causing harm. These substances were primarily opioids, such as oxycodone and heroin, but also included benzodiazepines and antidepressants. In addition to substitution, 9.9% of the sample reported withdrawal symptoms after using kratom. The consumers generally perceived their withdrawal symptoms to be milder than, but similar to, those caused by withdrawal from opiates. Only five percent of the sample reported tolerance to kratom, including a willingness to take higher doses in order to achieve the same effect. Finally, 4.3% of experience reports referenced hangover-like symptoms such as headache and nausea on the day after ingestion of kratom.

3.5.2 Dr. Oliver Grundmann Preliminary Report on Kratom Use and the Health Impact of Kratom Consumption – An online anonymous survey

Concluding our analysis of CSA Factor 5 is a summary of a few of the particularly relevant findings from the most comprehensive, relevant, and well-designed systematic internet survey of kratom users that has been done. It includes information from more than 9550 kratom users collected in October of 2016. The survey was designed "to provide [data for] stakeholders involved in kratom regulation, consumption, and current availability to better understand the current users statistics and the impact of kratom on health and specific conditions" in the US.

This survey was conducted by Oliver Grundmann, PhD, Department of Medicinal Chemistry, College of Pharmacy, University of Florida. Dr. Grundmann is Clinical Associate Professor of Medicinal Chemistry, and co-author of the Warner et al. review relied on in this 8 Factor Analysis. The study was conducted with the approval of the University of Florida Institutional Review Board. These findings have been extracted from a preliminary analysis of the report that is in preparation for publication by Dr. Grundmann, and the following summary was approved by Dr. Grundmann for inclusion in this 8 Factor Analysis. It is the opinion of the authors of this analysis that these findings and many other findings in the Grundmann study are highly relevant to consideration of the appropriateness of kratom for CSA scheduling, and that the findings would also be invaluable to FDA in its potential consideration of kratom's profile of consumption, effects, and health impact in the community. We encourage FDA, NIDA, and DEA to consult with Dr. Grundmann for a more extensive presentation of these findings if actions are considered prior to their publication.

Dr. Grundmann describes the general nature and intent of the study as follows*: "It is intended to provide stakeholders involved in Kratom regulation, consumption, and current availability to better understand the current user statistics and the impact of Kratom on health and specific conditions. It is not meant to be comprehensive or necessarily reflect the breadth of specific beneficial and adverse effects of Kratom. Rather, it serves as a basis for further research and to provide all stakeholders with a current snapshot of Kratom use in the US."*

Total # of respondents who consented to participate: 9,550

Age range: 54.17% were between the ages of 31-50, 29% younger than 30

Gender: 42.75% of respondents were female

Marital status: 1/3 were single/never married, 53.37% are married or partnered

Race: predominantly (89%) white

Employment: 57% employed for wages, 15% self-employed, 6% homemakers, 3.5% retired

Insurance coverage: 47% insurance through employer, 14% insurance through self-employment, 14.4% no insurance, 15.5% Medicare or Medicaid

Education: 82% at least some college (AA) or higher

Household income: 15% 35K-49K, 18.8% 50K-74K, 28.2% 75K and higher

The following findings are considered by Henningfield and Fant, and other PinneyAssociates experts to be particularly important in helping FDA in its evaluation of kratom given the size, scope, and design of the study and the fact that these variables are highly relevant to understanding reasons for consumption, consequences of consumption, and the consequences of a regulatory action that would prevent such individuals from obtaining kratom products. The Grundmann survey provides additional and complimentary information to the American Kratom Association's collection of testimonials from Kratom users (Attachment A), and would seem to provide an important quantitative basis for understanding the representativeness of those testimonials and for projecting to the broader population of perhaps 2 million or more American kratom users.

About 84% of the respondents self-reported good to very good health.

About 98% reported "currently" using kratom-containing products.

About 61% reported consumption in the form of powdered kratom consumed with a beverage or self-prepared kratom tea.

Less than 1% used store-bought liquid kratom (shot).

About 21% experienced some negative effects and these were predominantly nausea, constipation and other GI related.

Less than 1% reported needing health care treatment "because of your kratom use."

About 98% reported that a ban on kratom would negatively affect them.

Whereas most would support "regulating the quality of kratom products on the US market" about 90% answered "no" to the question: "Would you support categorizing Kratom as a medication that requires consultation with a pharmacist before purchase?"

Taken together, these and other findings reported by Grundmann provide a recent and informative characterization of kratom use and effects in the community, with the vast majority of the nearly 10,000 respondents reporting consumption for varied benefits, intake likely limited by undesired but apparently mild and tolerable GI and other effects, and little evidence of effects of medical or public health concern. The reports support the conclusion that removal of kratom from the market would be viewed highly negatively and the demand would likely drive many to illicit sources of kratom.

3.5.3 Testimonials Regarding Benefits

Consistent with the survey cited above, Attachment A provides a number of testimonials from kratom users regarding the perceived benefits of kratom.

The testimonials provide qualitative and personal insights that complement the quantitative and qualitative survey of Dr. Grundmann. The profile that emerges is that kratom is consumed primarily for general and specific life and life-style enhancing reasons. For many, the reasons include its value as a natural remedy for ailments. These consumers believe that kratom is more satisfactory than conventional medicines with respect to apparent effectiveness and has fewer undesirable side-effects than conventional medicines. Interestingly, this is not because kratom is devoid of any side effects. Indeed, many consumers report apparently readily tolerable gastrointestinal effects including some “stomach upset,” mild nausea, and constipation that apparently function to limit intake but are acceptable and tolerated in a natural therapy. From the perspective of abuse potential, to the extent to which such effects serve to mitigate the dose escalation that is so prominent with many known substances of abuse, including opioids, this is a highly favorable profile that may be part of the reason that abuse and abuse potential in the community appears very low.

3.6 Factor 6: What, if any, risk there is to the public health

As mentioned earlier, kratom products have been widely marketed and consumed as dietary supplements and natural remedies since at least the early 2000s. In collaboration, the Centers for Disease Control and Prevention (CDC) and the FDA “estimated the number of emergency department visits for adverse events associated with dietary supplements in the United States using 10 years of data (from January 1, 2004, through December 3, 2013) from the 63 hospitals participating in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project conducted by the CDC, the FDA, and the Consumer Product Safety Commission” (Geller et al., 2015). Projecting from 3667 cases, they estimated an average of 23,005 such emergency department visits annually, with 2154 hospitalizations annually. One fifth of the supplement-related visits involved unsupervised ingestion by children. The vast majority of the emergency visits involved products used for weight loss, energy, and sexual enhancement involving substance such as kava, hydroxytryptophan, caffeine, ephedra, ginseng, and yohimbine root. Less than 2% involved products used for pain or arthritis relief and these included substances such as arnica, glucosamine, and pokeweed. None were reported to have involved kratom or mitragynines. This does not mean that there actually had been none involving kratom or mitragynines, but certainly the public health signal through this major reporting system was very small and not indicative of a major public health problem.

In a recent review of the toxicology of mitragynine and analogs, Ramanathan and Mansor (2015, p. 282) concluded as follows: "To date there have been no reports of fatal overdose of kratom *per se*. If there are such occurrences, they are probably the result of kratom products contaminated with synthetic adulterants." This is consistent with other reviews of kratom pharmacology, toxicology, and epidemiology (Warner et al. 2016). In fact, if kratom products were banned from the market, it appears likely that many users would turn to the illicit market that would immediately expand to meet the demand. In that marketplace, there would be no oversight by FDA and no basis for consumers to be assured of product purity and contents. Moreover, the illicit market is also a competitive marketplace. It is reasonable to assume that many illicit product manufacturers and distributors would be likely to spike their products with various other substances in order to support their claims such as "Special Product X" (possibly with added synthetic cannabinoids to provide claimed increased mood altering effects); "Special Product Relief" (possibly with added synthetic opioids to increase pain relief); "Special Product S" (possibly with added synthetic stimulants to increase the stimulant effects) and so on. Replacement of the licit market (and a licit market that would hopefully thrive with increased FDA oversight) with the illicit market would invariably precipitate public health problems, serious adverse events, and associated overdose deaths that would pose far greater risks to the public health.

Despite the availability of more concentrated kratom based solutions, the production of some swallowable products, and some smoking in Southeast Asia, consumption of oral liquids and leaf chewing appears to vastly predominate. In fact, use by injection of extracted and concentrated alkaloids and nasal insufflation are not reported in Southeast Asia despite the fact that such routes (as well as smoking) are common in the same regions for opioids. This is another similarity with caffeine, which theoretically could be concentrated and injected, as has been done in human research (Garrett and Griffiths, 2001), yet globally the oral liquid consumption overwhelmingly predominates. Efforts to intensify the effects of kratom products by the approaches typical of opioids and stimulants, namely by injecting and snorting, have not been reported. Although there have been some reports of leaf smoking in Southeast Asia, this does not appear to be a common practice and consumption by smoking has not been reported in the US. This is consistent with the relatively low apparent intrinsic attractiveness of the alkaloids to persons who abuse drugs and are typically seeking strong stimulation, intoxication, sedation, and/or euphoria as can be produced by prototypical drugs of abuse such as amphetamine and cocaine types of stimulants, alcohol and controlled sedatives, and scheduled opioids, but are not found with kratom.

3.6.1 American Association of Poison Control Centers' National Poison Data System (AAPCC-NPDS)

The AAPCC-NPDS is considered a timely and sensitive system for tracking the emergence of trends in use-related effects and for capturing relatively low frequency events. From 2000 to 2005, a total of two (2) kratom-related exposures were reported to AAPCC; however, from 2010 to 2015, a total of 660 kratom-related calls were received (increasing from 26 in 2010 to 263 in 2015).[6] Kratom has not yet reached the threshold for inclusion as a separate product in annual AAPCC reports. The most recent report currently available is 2014. While the number of kratom calls for 2014 is not known, a reasonable proxy would be the 263 known kratom-related calls from 2015. In comparison, there were 55,151 diphenhydramine[7]-related calls, 18,470 aspirin[8]-related calls, and 1,355 nicotine pharmaceutical-related calls in 2014 (e.g., nicotine gum, patch, and lozenge).

3.6.2 Pediatric/Child (less than 6 years of age) exposure related adverse events and deaths.

An important consideration in public health and safety is the risks to children. Simply stated, we have been unable to document any deaths related to kratom exposure in children, or even evidence of serious adverse events or emergency department admissions for children attributed to kratom product exposure. This has included a review of federal surveillance systems including the AAPCC-NPDS described above, and internet searches for local and national media that typically report such events as news stories. This does not mean that no such events have occurred, but it does suggest that the signal is very weak and that any exposures that have occurred have not been associated with severe consequences. The rates of exposures and adverse events in children, which are apparently below the threshold of detection, are particularly striking in that they do not reflect a dearth of marketed and sold products. To the contrary, kratom products are sold by an estimated 10,000 vendors, and purchased, prepared, and used by millions of Americans in a wide variety of products constituting an approximately 200 million dollar market. Furthermore, to date there has been minimal guidance from FDA concerning packaging, allowable alkaloid content of manufactured products, labeling, and other guidance to minimize risks and promote safe storage and disposal. This is not an argument against such FDA oversight. To the contrary, appropriate guidance and regulation would be expected to help sustain low rates of inappropriate exposures and to minimize unintended consequences in children and adults. Nonetheless, the absence of adverse events in children and low prevalence of serious adverse events in adults is testament to the apparently intrinsic low hazard potential of kratom as marketed and used in the US.

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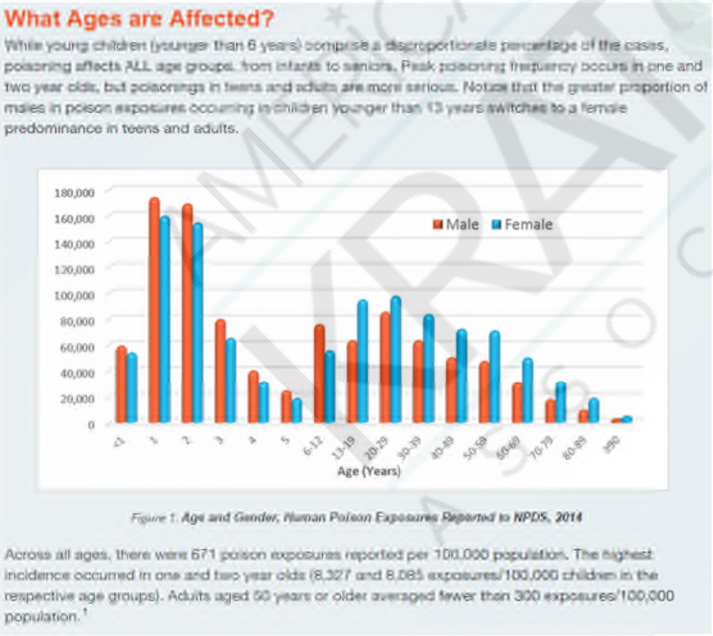
[6] http://www.cdc.gov/mmwr/volumes/65/wr/mm6529a4.htm.

[7] Diphenhydramine alone or in combination

[8] Aspirin only; does not include combination products

The following figures are from the National Capital Poison Center (2016). These are provided to illustrate the importance of considering children under age 6 as a crucial population in evaluating the safety of opioids, and to provide in this report a context for the evaluation of the health impact and safety of kratom.

This figure does not reflect or include any kratom-related poisonings since none had been reported by publication of these data.

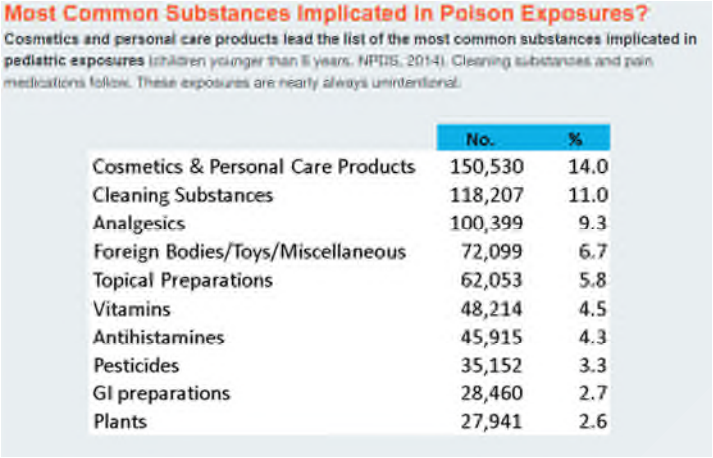


What Ages are Affected?

While young children (younger than 6 years) comprise a disproportionate percentage of the cases, poisoning affects ALL age groups, from infants to seniors. Peak poisoning frequency occurs in one and two year olds, but poisonings in teens and adults are more serious. Notice that the greater proportion of males in poison exposures occurring in children younger than 13 years switches to a female predominance in teens and adults.

Figure 1. ***Age and Gender, Human Poison Exposures Reported to NPDS, 2014***

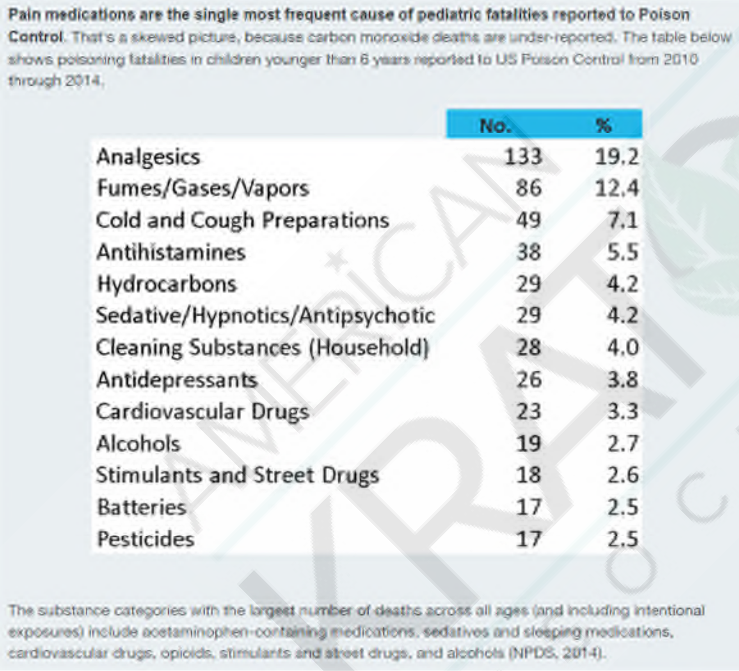
Across all ages, there were 671 poison exposures reported per 100,000 population. The highest incidence occurred in one and two year olds (8,327 and 8,085 exposures/100,000 children in the respective age groups). Adults aged 60 years or older averaged fewer than 300 exposures/100,000 population.[1]



Most Common Substances Implicated in Poison Exposures?

Cosmetics and personal care products lead the list of the most common substances implicated in pediatric exposures (children younger than 6 years, NPDS, 2014). Cleaning substances and pain medications follow. These exposures are nearly always unintentional.

	No.	%
Cosmetics & Personal Care Products	150,530	14.0
Cleaning Substances	118,207	11.0
Analgesics	100,399	9.3
Foreign Bodies/Toys/Miscellaneous	72,099	6.7
Topical Preparations	62,053	5.8
Vitamins	48,214	4.5
Antihistamines	45,915	4.3
Pesticides	35,152	3.3
GI preparations	28,460	2.7
Plants	27,941	2.6



Pain medications are the single most frequent cause of pediatric fatalities reported to Poison Control. That's a skewed picture, because carbon monoxide deaths are under-reported. The table below shows poisoning fatalities in children younger than 6 years reported to US Poison Control from 2010 through 2014.

	No.	%
Analgesics	133	19.2
Fumes/Gases/Vapors	86	12.4
Cold and Cough Preparations	49	7.1
Antihistamines	38	5.5
Hydrocarbons	29	4.2
Sedative/Hypnotics/Antipsychotic	29	4.2
Cleaning Substances (Household)	28	4.0
Antidepressants	26	3.8
Cardiovascular Drugs	23	3.3
Alcohols	19	2.7
Stimulants and Street Drugs	18	2.6
Batteries	17	2.5
Pesticides	17	2.5

The substance categories with the largest number of deaths across all ages (and including intentional exposures) include acetaminophen-containing medications, sedatives and sleeping medications, cardiovascular drugs, opioids, stimulants and street drugs, and alcohols (NPDS, 2014).

As summarized above, many types of products are routinely reported as child exposures to poison control centers. Kratom-related poisonings had not been reported to the NPDS at the time of publication of these data. The foregoing does not guarantee that exposure and adverse events will not occur in the future, even if they have not yet occurred. Despite efforts to minimize the risks and consequences of such exposures, across the nation, many children do and likely will continue to be able to ingest all nature of household and industrial products including cleaning products, agricultural products, glues, solvents, plants, chemicals, drugs, tobacco, nicotine liquids, and other potentially harmful substances. Minimizing such risks is a benefit of product regulation that ensures child resistant packaging as appropriate to the product, education, and labeling to ensure safe use, handling, and storage. Kratom products will presumably be evaluated by FDA to ensure appropriate packaging, labeling, and education; in that way, FDA can be confident that current and future kratom products pose minimal risks to children.

The following three plausible factors contribute to the apparent very low risk that kratom products pose to children, as well as to adults:

1. Low toxicity and harm potential of kratom and its alkaloids
2. Poor taste of even commercially marketed products with a commonly described “yuck” factor that would be expected to discourage consumption by children
3. Relatively low concentrations of alkaloids apparent in most marketed products and in raw leaf material

3.6.3 Ex-US Safety/Toxicity Data

Kratom consumption is quite high in Southeast Asia, with likely over 1 million regular adult users in Thailand alone. Heavy use by laborers, plentiful and inexpensive supplies of raw material, and hundreds of years of history of use have provided both experience in consumption as well as countless millions of exposures and opportunities for overdose deaths and other serious adverse health consequences if there were a high risk of such. Yet fewer than 100 serious adverse events associated with kratom consumption have been reported from Southeast Asia. A limitation of safety data from Southeast Asia is that much kratom consumption likely occurs in rural areas with limited reporting systems. Nonetheless, in contrast to opioid abuse and dependence, kratom consumption is not considered a major public health problem.

In an exploratory ethnographic survey of 149 long-term regular users of kratom (who chewed the leaves) in Thailand, the percentage of users reporting the negative effects of using kratom was relatively low (4–14% of all users) (Assanangkornchai et al., 2007). The negative effects included a perception of less productivity, a decreased sexual drive, fatigue, poor health, wasteful spending habits, dizziness, poor concentration and distractedness, difficulty sleeping, wasting working time, irritability, poor thinking ability, impaired memory, laziness, and social withdrawal. The perceived benefits of kratom consumption included helping users work longer and harder, feeling happy/sprightly, maintaining a good mood, sleeping soundly, and being healthy. In Thailand, the benefits of consumption, as reported by users and nonusers alike, appear to predominate over the negative effects, although these conclusions come from research that is more ethnographic characterization than clinical trial type research.

The safety of low doses of MG has also been evaluated in animal toxicology studies. Hassan and colleagues (2013) reviewed the data on the toxicology of MG as follows: In animal models, the toxicity of MG was claimed to be relatively low. Macko and colleagues (1972) found no evidence of toxicity, measured as tremors or convulsions, at doses as high as 920 mg/kg in dogs. A more recent study in rats reported lethal effects of 200 mg/kg total alkaloid extract of M. speciosa given intragastrically (Azizi et al., 2010). The actual amounts of MG as compared to other alkaloids were not reported by Azizi, and the specific relevance to human safety is limited, because humans consume far less than 200 mg/kg. Janchawee and colleagues (2007) reported lethal effects after an oral dose of 200 mg MG in rats.

Sabetghadam and colleagues (2013) administered three doses of MG (1, 10, 100mg/kg, p.o.) to rats for 28 days respectively. The groups of rats treated with the lower and intermediate doses showed no toxic effects during the study. Only relative liver weight increased after treatment with the high dose of MG (100mg/kg) in both the male and female treatment groups of rats. Biochemical and hematological parameters were also altered, especially in the high dose treatment group, which corresponds to the histopathological changes. Another study, also mentioned below in a summary of addiction potential studies is relevant to safety although it was designed to assess physical dependence and withdrawal at very high dosage relative to typical human consumption (Yusoff et al., 2016). Laboratory rats were given 30 mg/kg/day i.p., equating to an oral dose of about 990 mg/kg – equivalent to over 800 human 2-ounce doses. Some evidence of dependence and withdrawal were demonstrated but not lethality.

3.6.4 Deaths Possibly Involving Kratom

To date, there have been no reports of fatal overdose from kratom *per se* (Raffa, 2015, and references cited therein). Although there has been little systematic study of the pharmacodynamic effects of kratom, there is little clinical or scientific evidence of respiratory depression, and this would be consistent with the absence of documented overdose deaths attributable to kratom. Fourteen deaths potentially related to kratom had been reported globally until the DEA August posting in the Federal Register (see below). Of these, nine occurred in Sweden and appeared to have been related to consumption of an herbal blend called Krypton that was adulterated with O-desmethyltramadol, an active metabolite of the analgesic drug tramadol, which has been documented to carry a risk of severe respiratory depression and overdose death (Backstrom et al., 2010). The other five, three in the US, one in Norway, and one in Thailand, included co-administration of other drug substances. As a result, the actual cause of death is not clear.

In its analysis, DEA reported the following regarding deaths related to kratom in its Factor 6 analysis:

> *Deaths related to kratom exposure have been reported in the scientific literature beginning in 2009-2010, with a cluster of nine deaths in Sweden from use of the kratom product "Krypton' (Kronstrand et al, 2011). Since then, five more deaths related to kratom exposure were reported in the scientific literature (Holler et al., 2011, Neerman et al., 2013, Karinen et al., 2014, McIntyre, 2015, Anwar et al., 2016), and at least 16 additional deaths connected to kratom exposure, have been confirmed by autopsy/medical examiner reports (mitragynine and/or 7-hydroxymitragynine were identified in biological samples). Of these deaths, 15 occurred between 2014 and 2016 (citing Autopsy/Medical Examiner (ME) reports on file with DEA).*

DEA has not made available information that would enable assessment of the basis for concluding that kratom was "connected" to the "16 additional deaths" (beyond the 14 discussed above and elsewhere (Henningfield, 2015; Warner et al., 2016)). As demonstrated by the referenced sources in the DEA document, there has never been a published report in the literature of a death solely attributable to kratom, but rather these reported cases involved the ingestion of kratom along with pharmaceuticals or controlled substances known to present risk of death. These reports as summarized by the FDA document seem to agree with the general finding that these deaths were not solely attributable to kratom and generally leave the potential role of kratom unclear. For example, in the case of the nine deaths in Sweden occurring late 2009 to early 2010, the product ingested was not pure kratom, but rather a product called "Krypton." Laboratory analyses identified mitragynine and O-desmethyltramadol (known substances in Krypton blend) and other substances in blood samples of the deceased (Kronstrand et al., 2011). Several other cases of deaths involving multiple drugs are described in the DEA review as described in the table below. The contributing role of kratom, if any, cannot be ascertained, and interpreting these as "kratom-caused" or "Kratom overdoses" is certainly beyond the evidence.

Source	Drugs Involved
Neerman et al. (2013)	Mitragynine and therapeutic levels of dextromethorphan, temazepam, 7-amino-clonazepam, and a slightly elevated level of diphenhydramine in blood samples
Karinen et al. (2014)	Mitragynine and 7-hydroxymitragynine, zipiclone, citalopram, and lamotrigine in blood samples
McIntyre et al. (2015)	Mitragynine, along with therapeutic levels of venlafaxine, diphenhydramine, mirtazapine, and ethanol
Medical Examiner for Palm Beach, Florida (2014)	Mitragynine along with venlafaxine, fentanyl, amphetamine, and caffeine
Medical Examiner for Dekalb County, GA (2015)	Mitragynine, along with fentanyl, benzodiazepines, and cannabinoids

Medical Examiner for San Diego, CA (2015)	Mitragynine, along with methadone and alprazolam
Medical Examiner for San Diego, CA (2015)	Mitragynine, fentanyl, alprazolam, and an active clonazepam metabolite
Medical Examiner for San Diego, CA (2015)	Mitragynine, along with alcohol, benzodiazepines, and opiates

There was also a case of suicide in 2016, in which a 56-year old man was found with a self-inflicted gunshot wound to the head. The decedent had a history of alcohol and drug abuse. Laboratory analyses identified mitragynine and caffeine in blood samples. The cause of death, as determined by the Medical Examiner, was gunshot wound to the head. It is doubtful that consumption of kratom was in any way related to this death.

There were, however, three cases reported in the DEA analysis (DEA, 2016) in which kratom appeared to contribute to the death, though the mechanisms are not clear and the nature of the deaths seemed widely varied, possibly reflecting chronic heavy consumption of kratom and possibly other substances, as opposed to overdose death caused by opioid respiratory depression. One was a case of severe hypoxic encephalopathy complicating apparent mitragynine toxicity. The second case was determined by the Medical Examiner to be acute mitragynine (kratom) intoxication. The amount of mitragynine found in the liver was 200 times more than reported by McIntyre et al. (2015), where mitragynine intoxication was concluded to be the primary cause of death. In the third case, kratom products (“Green Malaysian”, “Yellow Vein Maeng Da”, and “Red Borneo”), and vials labeled U-47700 were found at the scene of the death. Laboratory analyses of blood samples identified the presence of mitragynine and the opioid antagonist naloxone. The cause of death, as determined by the Medical Examiner, was probable polypharmacy overdose.

A recently published, peer-reviewed article outlines well the position of the published studies: “Although death has been attributed to kratom consumption, there is no solid evidence that kratom was the sole contributor to an individual’s death” (Warner et al., 2016). We do not rule out the possibility that there have been overdose deaths involving extremely high doses of kratom; however, to date, we have been unable to document a single death in which kratom overdose can reasonably be concluded to have been “causal” in the death. By any measure this is in stark contrast with what has been documented for most recognized drugs and substances of abuse. For example, CDC reported data for 2014, with limitations acknowledged, in which deaths were reasonably concluded to have been categorized substantially, if not exclusively, to an opioid (28,647 in 2014 or nearly 80 per day) or other drugs most notably including sedatives, alcohol, and stimulants (18,408 or about 50 per day) for a total of 47,055 or about 129 per day (Rudd et al., 2016).

As mentioned earlier the very low risk of overdose poisoning and serious adverse events does not mean that they have not and will not occur. However, given the two decades during which consumption has increased to an estimated two or more million consumers in the US, in addition to far more extensive consumption in Southeast Asia, this is a substance and category of product with a remarkable safety record. It is not the profile of a serious or emerging public health problem that warrants drastic actions that would prohibit kratom consumers from continuing to lawfully purchase kratom. The safety record is all the more impressive given that kratom products have been marketed, prepared, and consumed without the level of regulatory oversight that is present for many other dietary supplements and natural products under the FDCA. Balanced and appropriate regulation seems vital to maintain the safety record. This should be accompanied by increased surveillance to better guide kratom regulation going into the future.

3.7 Factor 7: Its psychic or physiological dependence liability

There have not been adequate studies of physical or psychological dependence or abuse potential in humans caused by kratom. MG in high doses has been shown to produce physical dependence in rats. Yusoff et al. (2016) tested rats that received MG (30 mg/kg; i.p.) for 14 days and observed increased locomotor activity after withdrawal. MG induced a sensitized locomotor activation, which was significant after 7 and 14 days of treatment. There were no effects on locomotor activity during the subsequent three days of withdrawal. On measures of anxiety during withdrawal, the authors found no effects on anxiety after 12 hours of abstinence. However, after 24 hours and 48 hours, there was a significant decline in open arm time suggesting withdrawal-induced anxiety. MG withdrawal induced a paw tremor, body tremor, wet-dog shakes, ptosis, piloerection, teeth chattering, and grooming 12 hours after withdrawal. Except paw tremor and grooming, all effects were still present 48 hours after withdrawal. Most of the effects disappeared after 72 hours. The 30 mg/kg injected dose in this study would equate to an oral dose of 990 mg/kg. Converting this to a human equivalent dose based on body surface area, this would equate to approximately 160 mg/kg in humans, or over 11 grams of MG taken orally by a 70 kg human. The total alkaloid content in kratom leaves ranges from 0.5 to 1.5% (Hassan et al., 2013). Mitragynine makes up approximately 60% of this extract (Prozialeck et al., 2012; Philipp, et al., 2010; Kapp et al., 2011). Based on this, 1 gram of kratom leaves would contain around 15 mg of alkaloids (based on the 1.5% figure), about 9 mg of which would be MG. This would suggest that a human would need to consume over 1,200 grams of kratom leaves (or extract) to obtain a reinforcing effect – equivalent to over 1,000 2-ounce doses. Although kratom leaves also contain smaller quantities of other alkaloids including 7-OH-MG, which is more potent at the mu opioid receptor, very large quantities of kratom would have to be consumed to even see the levels of withdrawal seen in rats in this study.

Suwanlert (1975) reported that the chronic exposure to M. speciosa preparations can be followed by withdrawal symptoms in humans. Typical withdrawal symptoms include hostility, aggression, excessive tearing, inability to work, aching of muscle or bones, and jerky limb movements. Anxiety, restlessness, tremor, sweating, and craving for M.

speciosa were some of the withdrawal symptoms caused by M. speciosa dependence in an elderly man with an additional history of alcohol and anxiety disorder (McWhirter and Morris, 2010). Given mitragynine affinity to μ-opioid receptors, it is tempting to speculate that dependence and withdrawal syndromes may be mediated via this pathway. Although descriptive reports suggest that M. speciosa users might become addicted (Suwanlert, 1975), scientific reports on the rewarding properties of the plant or its active compounds are scarce at present.

Clearly there is a need for more clinical and nonclinical research on the behavioral and physiologic effects and abuse/dependence liability of kratom. It is not completely devoid of signs that could be consistent with abuse or dependence, but neither is there evidence of high abuse/dependence potential that would support the conclusion that CSA scheduling is indicated.

3.8 Factor 8: Whether the substance is an immediate precursor of a substance already controlled under this subchapter

Neither kratom nor any of the constituents in kratom or its alkaloids are controlled substances or are precursors of a controlled substance.

4 Recommendation

After consideration of the eight factors indicative of control in the CSA, a substance must be found to meet three findings “required” for placing the substance in a particular schedule. 21 USC 812(b). These finding relate to the substance’s abuse potential, its physical or psychological dependence liability, and its accepted medical use in the United States.

4.1 Kratom’s potential for abuse is consistent with unscheduled substances

In evaluating the potential for abuse of kratom and its alkaloids, the history of consumption in Southeast Asia spanning centuries in addition to the decades of use in the U.S. reveals a pattern of volitional use with very little evidence of actual abuse. The history of use is consistent with the pharmacology of kratom and more specifically its alkaloids (MG and 7-OH MG), which produce mixed pharmacological effects that are generally mild and consistent with the stimulant-like effect of caffeine. The combination of pharmacology and pattern of actual use demonstrate that kratom’s abuse potential is consistent with that of other unscheduled substances.

Mitragynine is an indole-containing alkaloid that is structurally similar to yohimbine, the primary component of yohimbe extract, which is legally marketed in the United States as a dietary supplement. Although the pharmacology of mitragynine and 7-OH-MG are still being studied, the most recent analysis gives significant reason to think that the pharmacology would predict low potential for abuse. In particular, analysis by Kruegel et al. (2016) shows that mitragynine is only a partial agonist of the human μ-opioid receptor, and in fact acts as an antagonist to the δ- and κ-opioid receptors. Kratom's only partial agonist activity, specificity to the human μ-opiod receptor, antagonist activity to the δ- and κ-opioid receptors, and mechanism of action are all consistent with other partial agonists that "display less respiratory depression, tolerance development, and constipation" (Kruegel et al., 2016). Indeed, an absence of reports of respiratory depression or dose escalation characterizes the observed use patterns of kratom, as detailed below. Although 7-OH-MG appears to have some stronger agonist characteristics, it is less than 2% of the crude base and "is unlikely to generally account for the psychoactive properties of this plant" (*Id.*). Nor could either MG or 7-OH-MG be extracted from kratom without sophisticated equipment and chemistry training. As a result, the pharmacology predicts a potential for abuse on par with other unscheduled substances.

The observed patterns of use in the United States confirm the prediction of the pharmacology: kratom's use patterns in the United States reflect volitional use for desired effects and are inconsistent with abuse. In assessing kratom's potential for abuse, the history of use stretching back decades in the United States, and centuries in Southeast Asia, provide ample data to establish the patterns of use of the product. That history is notable for the absence of many indicia of abuse, such as impaired control over use, compulsive use, and continued use despite harm. Federal surveys on drug abuse have not detected a significant signal regarding abuse of kratom. This reflects not only a dearth of abusive use, but also a lack of individuals seeking treatment or therapy for addiction. Reports of poisonings and deaths remain very rare and are complicated by comorbidities and exposure to other substances; remarkably, no deaths, serious adverse effects, or emergency department exposures have been reported in children. Accordingly, the patterns of use do not reflect significant actual or potential for abuse.

In contrast, kratom consumers describe mild effects characterized by alertness and mood enhancement, comparable to the effects of coffee and other caffeine containing beverages and dietary supplements. Consumers also sometimes report increased sociability, again comparable to that experienced with caffeinated beverages. Kratom consumers have not been observed to engage in intravenous, intranasal, or inhalation abuse of the substance,[9] nor have there been significant reports of binging. Instead, kratom consumers commonly consume kratom as a tea or else sprinkle the substance on foods. The actual patterns of use and effects are comparable to those of other unscheduled substances, including coffee, tea, and other dietary supplements.

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[9] FDA has previously concluded a substance has a lower potential for abuse when it is only consumed orally and is not abused by "other routes of administration, either intravenously, intranasally, or by

The assessment of a substance's potential for abuse is an inherently comparative assessment and requires consideration in the context of other comparable substances. In this regard, kratom's potential for abuse is equivalent to, or lower than, that of a variety of unscheduled substances. For example, the FDA-approved drug Contrave® contains the substance bupropion, which has been shown to have properties consistent with "feelings of euphoria and drug desirability" (Contrave Prescribing Information (PI) at § 9.2). In a section labeled "Abuse," the FDA-approved PI for Contrave states that bupropion caused agitation/excitement, "produced mild amphetamine-like activity," and scored between placebo and amphetamine on a liking scale (*Id.*). Nevertheless, FDA did not recommend scheduling bupropion – as the substance's mild characteristics of abuse potential can be sufficiently managed through regulation under the FDCA.

Likewise, FDA declined to recommend scheduling of dextromethorphan, despite multiple characteristics of a drug of abuse that appear to far exceed kratom's potential for abuse. Dextromethorphan is a substance chemically related to the opioid codeine and is used as an ingredient in many cough suppressants available as over-the-counter (OTC) drugs. In that way, dextromethorphan, like kratom, is readily available for consumer purchase. DEA has determined that dextromethorphan is associated with "[e]uphoria and hallucinations" and significant intoxicating effects, including "hyperexcitability, lethargy, ataxia, slurred speech, sweating, hypertension, and/or nystagmus" (DEA Office of Diversion Control, *Dextromethorphan*, Mar. 2014).[10] According to the 2014 DEA factsheet, dextromethorphan has been the subject of 45,748 Poison Control Center case mentions, 33,811 single exposures, and six deaths. *Id.* Likewise, analysis by FDA found that although the drug was not "widely abused," it demonstrated a propensity for abuse and "intentional misuse for abusive purposes." *See* Briefing Package for FDA Drug Safety and Risk Management Advisory Committee,

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inhalation of the smoked drug substance." FDA, *Basis for the Recommendation to Reschedule Nabilone from Schedule II to III of the Controlled Substances Act (CSA)* at 10 (Sept. 11, 1998). FDA recommended rescheduling Nabilone to schedule III, despite finding "an adverse reaction profile similar to delta^9-THC" and "delayed onset and longer duration of action of marijuana."

[10] The DEA factsheet is available at https://www.deadiversion.usdoj.gov/drug_chem_info/dextro_m.pdf.

Sept. 14, 2010.[11] Yet the recommendation of the Drug Safety and Risk Management Advisory Committee against scheduling,[12] and its continued absence from CSA scheduling, appears to reflect the understanding that the drug may be appropriately managed through FDCA regulation.

Nicotine is another example of a broadly marketed and used substance that meets criteria for CSA scheduling, and was determined by FDA to merit potential appropriate placement in Schedule III (e.g., Klein report of FDA analysis of CSA 8 Factors, 1994). It is present in many over the counter and prescription medicines for smoking cessation, which are used by millions of consumers in the U.S. The process of approval of a nicotine nasal spray for smoking cessation precipitated the convening of the FDA's Drug Abuse Advisory Committee and subsequently an evaluation by the Associate Commissioner for Health Affairs Dr. Stuart Nightingale and the Interagency Committee on Drug Control to consider whether or not nicotine nasal spray should be placed in the Controlled Substances Act (FDA, 1995, 1996). In brief, the Interagency Committee recommended, and FDA and NIDA concurred, that public health would be better served by not placing nicotine in the CSA.

There are many such examples of substances and products that may meet technical criteria for placement in CSA; however, the dextromethorphan and nicotine experiences are noteworthy for the deliberations in which it was clear that the more important questions were not *'could they be so placed?' (they clearly could) but rather 'should they be so placed?'* In other words, was public health better served by not scheduling them, but rather ensuring surveillance and oversight and appropriate regulation under the FDCA? In these cases and many others involving prescription and over the counter medicines and dietary supplements the answer has been that public health is often better served by not scheduling substances and products that could be scheduled. In other words, public health is often best served by applying the most appropriate regulatory tools.[13]

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[11] The package is available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM224446.pdf.

[12] *See, e.g.*, Kerri Wachter, *FDA Panel Recommends That Dextromethorphan Not Be a Scheduled Drug*, Internal Medicine News (Sept. 14, 2010), *available at* http://www.mdedge.com/internalmedicinenews/article/17801/adolescent-medicine/fda-panel-recommends-dextromethorphan-not-be.

[13] By disclosure and way of experience, Dr. Henningfield participated in the nicotine considerations representing NIDA and serving on Commissioner Kessler's interagency tobacco and nicotine working

Similarly, the botanical dietary supplements St. John's Wort, Valerian, and Kava Kava have not been scheduled, despite the fact that all three are known to have "reinforcing effects," act as sedatives, and have been the subject of hundreds or thousands of calls to Poison Control Centers in the past six years. Nor have guarana or kola nut been placed into a schedule under the CSA, despite the fact that both are used for increased energy and have certain characteristics of a drug of abuse. The inevitable conclusion from the decisions not to control these substances is that not every substance with characteristics potentially indicative of mild abuse potential merit scheduling, but rather that these substances can be adequately regulated through the existing authority of the FDCA.

The long history of use of kratom demonstrates a pattern of use consistent with other consumer products such as coffee and botanical dietary supplements. The history of use combined with the pharmacology of kratom lead to the conclusion that kratom has a very low potential for abuse, and that its abuse potential is on par with, or lower than, other unscheduled substances.

4.2 Kratom has a dependence liability consistent with unscheduled substances

As described in this 8-Factor Analysis, kratom overall has a low potential for abuse, dependence, and public health harm, and consideration of all 8 factors does not provide a compelling case that kratom should be placed in the CSA. The data show little tendency among kratom consumers to increase their dose to their personal detriment or to the point of addiction, as is indicative of growing dependence. Furthermore, the data demonstrate that increasing the dose of kratom is more likely to produce undesirable gastrointestinal effects, constipation, and lethargy, with little additional mood enhancement. There have been no reports in TEDS of consumers seeking treatment for dependence, nor have treatment clinics recommended monitoring such reports. These typical indicators of dependence – increased dosing and dependence treatment – are not present with kratom, which strongly suggests that its dependence potential is low or even negligible.

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group, and Dr. Nightingale's committee, on the nicotine scheduling issues in 1994-1996, as well as in NIDA's recommendations against scheduling nicotine gum and patch products. Dr. Henningfield and other members of PinneyAssociates developed the 8-Factor Analysis of dextromethorphan for the Consumer Healthcare Products Association that supported its position that although dextromethorphan met criteria for scheduling, public health would be better served by more appropriate regulation, and surveillance, and efforts by product manufactures to discourage inappropriate use, and this position was supported by FDA's advisory committees and ultimately FDA itself.

Nor are observed reinforcing effects indicative of physical or psychological dependence. The reinforcing effects are described as mild and comparable to caffeinated beverages such as coffee or tea. These mild reinforcing effects are unrelated to physical dependence, and do not rise to the level of even limited psychological dependence. In addition, due to the very low bioavailability of MG and 7-OH-MG (only 3.03% bioavailable in kratom), huge quantities of kratom would need to be consumed to obtain the effects seen after taking a pure mu opioid such as morphine. The result is that kratom shows a very low dependence profile comparable to or lower than that of other unscheduled substances.[14]

Notably, the dependence liability finding necessary for control under CSA does not direct an analysis of dependence generally, but rather dependence liability based on “abuse” of the product. *See* 21 USC 812(b). As discussed above and demonstrated by this analysis, there is very little actual or potential abuse of kratom. Not only does consumer use of the product not cause dependence, but it also does not rise to abuse, which is the focus of the CSA in assessing dependence liability.

4.3 As a Matter of Law, Kratom Should Not Be Scheduled

The final finding for scheduling a drug or substance relates to its currently accepted medical use. 21 USC 812(b). The currently accepted medical use of a pharmaceutical drug is often straightforward, and FDA (or DEA) can easily establish whether a pharmaceutical drug has a currently accepted use in treatment of patients. Less clear is how this criterion may be applied to a non-pharmaceutical substance, such as a dietary supplement. A dietary supplement is a product intended to supplement the diet that contains certain types of ingredients, including botanical ingredients, and is not approved or authorized for investigation as a drug. 21 USC 321(ff). Consistent with the regulatory scheme of the FDCA, a dietary supplement is not marketed with claims of efficacy for medical use – indeed, if a dietary supplement included such claims it would likely meet the standards for regulation as a drug product under the FDCA. *See* 21 USC 321(g)(1), 355(a). Accordingly, as a dietary supplement, while kratom has a long history of use in the US consistent with other well-known dietary supplements, it, like all other dietary supplements and a broad range of consumer products, does not have a currently accepted medical use as that term has come to be defined under the CSA.

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[14] *See, e.g.*, Memorandum from Dr. Catherine Dormitzer et al., FDA Epidemiologist, to Dr. Michael Klein, Controlled Substance Staff, regarding Abuse, Misuse, and Overdose of Dextromethorphan-Containing Products at 9 (Dec. 1, 2009) (describing 14 counts of “Drug Dependence” for dextromethorphan-containing products).

The CSA is specific in defining the three findings required to place a substance in each schedule, and except as required by international agreements and except for immediate precursors, "a drug or other substance may not be placed in any schedule unless the findings required for such schedule are made with respect to such drug or other substance." 21 USC 812(b). Schedules II through V all require a finding that the substance has a "currently accepted medical use in treatment in the United States." *Id.* In contrast, only Schedule I permits the scheduling of a drug without a currently accepted medical use, but Schedule I also requires a finding that the drug or substance has a "high potential for abuse" and a "lack of accepted safety for use of the drug or other substance under medical supervision." 21 USC 812(b)(1).

As written, the CSA requires that all three findings must be made to place a substance in a schedule; therefore, a substance that does not fit all three findings for any schedule cannot be placed in any schedule. 21 USC 812(b).[15] The Federal Circuit Courts of Appeals have applied this requirement. In *Americans for Safe Access v. DEA*, 706 F.3d 438, 442 (D.C. Cir. 2013), the DC Circuit stated that marijuana could not be rescheduled to Schedules III, IV, or V without a currently accepted medical use, because a currently accepted medical use is a requirement of those schedules. Likewise, in *Grinspoon v. DEA*, 828 F.2d 881 (1st Cir. 1987), the First Circuit found that all three findings are necessary before a substance maybe be scheduled. The court held that "[t]he CSA clearly provides that a substance may not be placed in Schedule I unless it lacks *both* a 'currently accepted medical use in treatment in the United States' *and* 'accepted safety for use… under medical supervision,'" *Grinspoon* at 887, and also found that "the CSA also requires substances identified for placement in Schedule I to have a 'high potential for abuse,'" *id.* at 892.[16]

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[15] A federal agency is bound by the plain language of a statue if that language is unambiguous or capable of only one interpretation. "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron v. Natural Res. Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984).

[16] While courts have discussed an alternative interpretation of the required findings for scheduling under the CSA, those cases have not resolved the issue as the ultimate ruling was on other grounds. *See Nat'l Org. for Reform of Marijuana Laws (NORML) v. DEA*, 559 F.2d 735 (D.C. Cir. 1977) (considering the notion that a substance that lacks an acceptable medical use may be placed in Schedules II-V, contemplating that the findings required by the CSA function more as considerations than findings); *NORML v. DEA*, 559 F.2d at 747-48 (citing a discussion in *United States v. Maiden*, 355 F. Supp. 743, 748-49 n.4 (D. Conn. 1973), in which the district court stated that the three findings could not be "cumulative" and that a drug with no currently accepted medical use should be placed in Schedule I, "whether or not the potential for abuse is higher than for other drugs, so long as the abuse potential is not minimal."); *NORML v. Bell,* 488 F. Supp. 123, 140 (D.D.C. 1980) (same).

A plain reading of the CSA language that "a drug or other substance may not be placed in any schedule unless the findings required for such schedule are made with respect to such drug or other substance" is also consistent with the purposes of the statute. The CSA was not intended to control every substance with any indicia that may indicate a potential for abuse, regardless of the nature of the substance. Instead, Congress was focused on certain kinds of substances, with others appropriately regulated by other federal and state statutory schemes. In fact, Congress expressly stated that the CSA is to be used to control substances that "have a *substantial* and detrimental effect on the health and general welfare of the American people." 21 USC 801(2) (emphasis added). Consistent with this approach, FDA and DEA have never scheduled consumer products with some characteristics in common with drugs of abuse, such as caffeine, herbs and other natural products, and solvents or household cleaners. Kratom, as a dietary substance, does not have an accepted medical use as that term is defined under the CSA, but it also does not have a high potential for abuse or a substantial and detrimental effect on the health or general welfare of the American people. It is another example of a substance that is outside the intended coverage of the CSA.

As reflected by the analysis of the 8 factors above demonstrating that kratom has an abuse potential and a dependence liability similar to other unscheduled substances, it is not necessary to diverge from the CSA requirement that all three findings must be made to place a substance in a schedule, because kratom's low potential for abuse, low risk for dependence, and impact on the public health demonstrate that it is not appropriate for control under the CSA and can be appropriately regulated comparably to other unscheduled substances outside of the CSA.

4.4 As a Matter of Public Policy, Kratom Should Not Be Scheduled

There are significant costs and tenuous benefits to scheduling kratom. The decision to schedule a drug commits significant governmental resources (including personnel for enforcement) at a great cost to be ultimately borne by the public. These resources are ultimately diverted from enforcing the CSA against the illicit use of other controlled substances – substances that, when compared to kratom, pose a far greater threat to the public health. Consumers of kratom will also bear the social costs of scheduling, and the consequences of enforcement or noncompliance are likely to fall at least in equal measure on the kratom users with the longest history of use, namely, immigrant families from Southeast Asia (JEH discussions with Hmong community members in Minnesota; Axelrod and Windell, 2012, p. 56). Like other kratom consumers who have safely integrated kratom use into their daily habits with no negative consequences to health, family, or work obligations, these communities may have difficulty accepting the scheduling of a substance with a long history of safe use among community members, and scheduling may contribute to a spike in illegality and attendant social ills. If kratom is scheduled, some consumers will inevitably turn to other products, including narcotic drugs, or underground sources of kratom that are not regulated for purity, quality, or accuracy of labeling claims. *See* Section 3.6. Other individuals may try to continue to use kratom despite scheduling, and ultimately end up in the criminal justice system because of the use of a product with very low risk to the individuals, their families, or their communities.

In exchange, no public health crisis is solved by scheduling kratom. As demonstrated in the analysis above, kratom use has not promoted crime or violence. It does not sap the productivity of consumers or jeopardize their health. Its effects are mild and are generally reported to involve alertness and mood enhancement, comparable to the effects of coffee. The product has low intrinsic attractiveness and has not been associated in published literature with single-substance deaths. The significant and detrimental impact of scheduling on government resources and, more importantly, consumers is not justified by kratom's effects.

Permitting kratom and its constituents to remain unscheduled does not abrogate all control over these products. Current FDA authority under the FDCA can be used to better ensure the purity and safety of the product available in the US marketplace, while scheduling under the CSA would divert resources from more critical initiatives, have a significant negative impact on kratom consumers, and do little to improve the public health. The FDCA provides FDA the authority to ensure that labeling of kratom products is not false or misleading in any particular. *See* 21 USC 343. This includes the requirement to accurately identify the product and any additional ingredients and to not misrepresent the MG or 7-OH-MG content of the product. FDA can also regulate misbranding of the product through claims made in labeling, including promotional advertising. Specifically, FDA retains the authority to take action against promotional claims that imply therapeutic use without sufficient supporting evidence. *See* 21 USC 352, 355. Nor is FDA alone in this endeavor. States may also take steps to appropriately regulate kratom, as they have done with a wide variety of other products not placed into a schedule under CSA. For example, some states have already set a minimum age to purchase or consume kratom,[17] and others are studying its effects to educate citizens and guide future policy.[18]

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[17] Currently Illinois and Louisiana restrict the sale of kratom to people over the age of 18. *See* 720 Ill. Comp. Stat. 642/5; La. Stat. § 40:989.3. New York is considering restricting its sale to people over the age of 21, *see* N.Y. Assembly Bill A9121, and North Carolina is considering restricting its sale to people over the age of 18, *see* N.C. S.B.830.

[18] AB 4431 is pending in New Jersey to restrict the sale of kratom. SB830 is pending in North Carolina and would require a study of kratom by state authorities. Neither state had taken final action on either bill at the time of writing.

5 Conclusion

We do not recommend scheduling of kratom or any of its specific alkaloids under the Controlled Substances Act. Kratom has a low potential for abuse and a low dependence liability and there is insufficient evidence of personal harm, adverse health effects or detriment to the public health to warrant control under the CSA. Effectively banning the availability of kratom through scheduling could precipitate public health problems that do not presently exist or are at very low levels, because this would shift the market place from a largely lawful retail market to illicit manufacturers and distributors with no regulated labeling, purity or content standards, or effective ability to remove adulterated products from the market. Appropriate regulation of kratom under the FDCA is the most effective way to protect the public health by ensuring appropriate access and oversight and to sustain the overall very low adverse personal and public health effects associated with kratom consumption.

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Attachment A: Testimonies of Kratom Consumers

This document contains the testimonies of responsible kratom users, as compiled by the American Kratom Association between September 19th and September 21st, 2016

My name's [redacted], I'm 32 years old and I was diagnosed with Multiple Sclerosis and Degenerative Disc Disease. For the past ten years I have undergone exhausting physical therapy sessions and counseling to deal with this illness and pain. Over the years my tolerance to opioid prescriptions has climbed and I made the decision, with the help of my doctors, to lower my doses as much as possible. In Spring 2016, a family member asked me if I had tried an herbal supplement called Kratom. I decided to give it a try as I was at a point where I'd be willing to try almost anything to get rid of the pain. After a week I noticed my energy levels were back to where they were four or five years ago, and in six weeks my pain had subsided enough to let me work 8 hours a day up from only two or three before. Kratom has helped me to become a productive member of society again.

My Name is [redacted]. I am a 39 yr-old PR & marketing consultant. I have never been arrested. I have never been “into drugs”. I am a business owner & productive member of society. I graduated magna cum laude from my university. I speak three languages fluently. I am the furthest thing from a “felon” or a “junkie”, yet I have suffered from depression and suicidal thoughts since adolescence. At one point I was on three different antidepressants. I felt like a ZOMBIE. I became listless, tired all of the time. A shell of a person. I have been taking Kratom for the past year and I can tell you without a doubt that the United States & the world gets way more out of me as a member of society in terms of productivity, positivity & contribution than if I had not discovered this incredible herb. I take very small amounts every day. Since I started taking it, I frequently go days at a time without it, and I do not suffer any withdrawals, but yes, the depression does come back. But the feeling is NOT like an “addiction” feeling (I’ve tried to quit coffee, I know what addiction feels like). It's more like my symptoms of depression come back within a few days. If the DEA bans this substance, honest, hard-working people who are MUCH more productive members of society thanks to Kratom will be unjustly turned into felons, just because they want a better life for themselves and the people around them. So if this passes, you then leave people like us with three choices: 1) suicidal depression 2) zombie listlessness on prescriptions meds that don’t work for us or 3) become a felon because we responsibly use a safe herb that is an incredible quality-of-life enhancer. If anybody in the DEA uses any sort of prescription drugs for any physical or mental ailment, I would like them to look in the mirror and ask themselves: how would you feel if by tomorrow you were considered a “felon” for taking that prescription? Feels unjust doesn’t it? More than that, it feels like a huge step back for society as a whole. I understand there are people out there who overdose on everything. There are people overdosing on paint thinner & “whipits” from whipped cream cans, for crying out loud! But those of us using Kratom responsibly deserve to have access to a safe herb that helps our quality of life like NO other supplement or medication does. For us, for this country, for society, and for people productively contributing to this economy...Please keep Kratom legal.

My name is [redacted], I’m a 35 year old (returning) nursing student that has been married for ten years with two kids under the age of 15. I have MS and degenerative disc disease.(Black Disk disease to be specific) While being treated for my disc degeneration, I was prescribed massive amounts of painkillers. This line of treatment made it impossible for me to care for my daughter (who was three at the time), and my blind veteran father. I will never forget the conversation with my doctor; he told me I had no choice in treatment options and that horrid unresponsive state was my new reality. To quote him “You need to have a conversation with God if you want to get better.” Then, by chance, I found Kratom. Once I started using this miraculous plant, I was able to come off the painkillers completely. I have since been diagnosed with MS and carpal tunnel syndrome. I have not missed a single day of work other than maternity leave because of the properties of kratom. During my maternity leave and for several days of testing a year, I intentionally miss my daily doses. The pain is excruciating. I can barely walk, the depression and anxiety that has come because of the MS is so fierce I am almost mentally paralyzed. To be sentenced back to that almost comatose state would be a fate akin to death. I am who I am, a mother, student, wife, daughter, money earning member of society, because of kratom.

My name is [redacted] [redacted]. [redacted]. I am a 44 year old female and up until March 2013 was employed as a federal police officer with the Federal Bureau of Investigation for 23 years. In 1996, I was diagnosed with systemic lupus and fibromyalgia, two chronic, life-long illnesses for which there is no cure. Lupus causes severe pain, stiffness, swelling, tenderness and warmth in your joints. Fibromyalgia symptoms are: deep muscle pain causes painful tender points, morning stiffness, sleep problems, fatigue and anxiety. For twenty years I have suffered daily with severe pain throughout my joints and muscles.
In the fall of 2014, after being on eleven medications (prednisone, Flexeril, Zanaflex, Nucynta, Lyrica, triamcinolone, Lortab, gabapentin, synthroid, Tramadol, and nortriptyline) that really didn't help and prescribed to me by my rheumatologist and pain management doctors, I started to suffer serious side effects (blurry vision, short term memory problems, dizziness, headaches, weight gain, and leg cramps) from the combination of the medications. At this point in my life, I decided to taper down off of all prescribed medications. Shortly thereafter, and still suffering from severe joint pain, a friend suggested that I try kratom. I immediately researched and learned as much as I could about it. After a month long quest to learn as much as I could, I finally got up the nerve to try it. That was the day that I got my life back prior to being sick. The joint pain was gone. I felt like a new person. I am a wife, sister, friend, aunt, and best of all, a mother to my twelve year old daughter again.

My name is [redacted] and I am 57 years old, I have been married for 36 years. I am the mother of three sons and grandmother of 3 beautiful granddaughters. I earned a college degree while working a full time job and raising our children. I have worked for the same company for over 35 years and currently hold the position of Senior Production Planner. I go to church every Sunday and I am a member of the choir. I am in good physical condition but have had arthritis in my knees for several years that I have treated with ibuprofen, Meloxicam, Tramadol for flare ups, and cortisone injections 2-3 times a year. A little over a year ago a family member suggested that I try kratom and I was amazed at how well it controls my pain without making me feel drugged - just completely normal and pain free! Since I started taking kratom I have stopped taking both ibuprofen and Tramadol, and have only had one cortisone injection in the last year.

My 59 year old husband retired in 2008 with 30 years of law enforcement at the rank of lieutenant. He was injured on duty in 1991 and as a result has had two fusion surgeries on his back. He has been in constant pain since then but has always resisted taking prescription pain medication because he does not like the way they make him feel. Since taking kratom he is also feeling and functioning much better now, working two part time jobs and is happy to be able to be productive with reduced pain.
I really can't say enough about this wonderful plant. I am now exercising regularly and I am about 15 pounds lighter than I was a year ago. I can now sit at my desk and work all day without hurting, and come home at the end of the day and take walks and play with my granddaughters instead of falling into my recliner until bedtime. I can work in my yard on the weekends and not be a burden to my children. I am much more active now than I was before taking kratom.
I know that our quality of life as productive members of society will not be the same without kratom. We have been hard working, tax-paying, law abiding citizens our whole lives and now the DEA wants to deprive us of the best option that we have found to treat our pain!

My name is [redacted] [redacted], I'm a 36 year old, father of two with one on the way. I am the sole provider for my family. I take Kratom to help with the pain and spasms associated with crohn's disease. It's helped me tremendously with managing the pain and some of the other symptoms that I have to deal with. I've been taking it for about 6 months now. It's a great alternative to the percocet prescribed by my

Doctor. No ill effects from the Kratom and no dependency. I only have positive things to say about it. Pain pills make me tired, depressed and they take me out of focus and they make you dependant. None of this is true about Kratom. I can now manage the symptoms associated with crohn's without the side effects of prescription medications. Prior to Kratom, I haven't had a solid stool in years, I didn't know I had crohn's until it got real bad and I had to have surgery to have a large section of my colon removed. Kratom has changed all that. A solid stool may not sound like something to get excited about, but to me, it means my gut is getting better! I think anyone dealing with this disease would want to know about it.

[redacted] [redacted]
FL

I am a 45 year old business owner who has been using kratom for 8 years. In 2001 I was diagnosed with atrial fibrillation and prescribed a plethora of pills in an effort to control it. I struggled with the side effects of those medications and the anxiety of dealing with a cardiac ailment that could cause problems in a moment's notice...there were many trips to the ER over the years. It affected my personal life as well as my professional life in the worst ways imaginable. Since using kratom regularly, I have not had a single issue with my heart rhythm. And best of all, not a single trip to the ER. I have no more of the negative side effects I experienced with drugs like beta blockers, digoxin and blood thinners. I am no longer terrified of leaving the house, no longer afraid of passing out (my blood pressure was dangerously low on betapace). I have a greater quality of life now more than I did. I am healthier, happier, more productive, and this plant has saved my life as far as I am concerned.

I am a law abiding citizen with zero criminal record, I volunteer my time and efforts to help others and kratom has given me a new lease on life. It also helps with intestinal inflammation that I struggled with, and anxiety - which is a big part of atrial fibrillation. Those are bonuses from using this plant regularly. I do NOT use this plant recreationally and I can guarantee you that I get more of a 'high' from cold medication at normal doses than I get from kratom. Banning this plant will take me back to square one: dealing with powerful, dangerous meds like digoxin and struggling to manage the dangerous side effects from the other meds that I will likely have to begin taking again. Please do not sentence me to have to deal with that struggle again. I solved it! Kratom allowed me to have my life again. Not being able to use it will literally be like turning the clock back on my health.

I am 38 years old, and I take kratom to help me manage depression, anxiety and menstrual cramps. I have tried Rx and OTC drugs, but the Rxs have horrific side effects and are not nearly as effective as kratom. The OTC meds also sometimes do not really reduce the pain I feel from cramps. Sometimes I feel so unwell I have to call off work. I do not like having to call off work. If this ban goes through, I know that my depression and anxiety will be so powerful and this is so scary. I see myself becoming weighed down with depression and anxiety and having to be in horrible pain once a month for cramps. It will be much more difficult to work each day, and I am sure I will have many more sick days if this ban goes through, maybe even having my job put at risk. I have an advanced degree with a professional job. I also see the quality of my life plummeting even outside of work. When I am depressed, anxious, or in pain, I don't want to go out, run errands, and I lose interest in hobbies, exercise, etc. Kratom helps me take on the day, so to speak. I have been using it for about 6 years and have found it to have such a positive effects on my physical and mental health. -[redacted]., [redacted] [redacted], CA

My name is [redacted]. I am now 44 but started taking Kratom at age 39 to help ease my debilitating headaches after working as a nurse. I suffered a brain injury. I found that not only did the herbal supplement help my headaches, it helped with my cognitive impairment as well. I injured my back during the initial fall and multiple times during seizures. Kratom helps ease that pain as well. If the Kratom ban goes through I would be forced to rely on opiates for my pain control and be faced with the very certainty of becoming dependent on these medications. It's bad enough that my career and driving ability was ripped away from me. Now I just fall into an even deeper depression over the little choices I have, also being taken away. Before I found Kratom I had attempted suicide 4 times, but haven't thought of it since. Thank you for hearing my story, [redacted], [redacted] [redacted] California

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My name is [redacted] [redacted]. I am 49 years old, I am a dad of four, married, a teacher and an ordained pastor with a Masters of Divinity from [redacted] Seminary. I graduated Magna Cum Laude from the University [redacted] [redacted] in 1989, and with Honors from [redacted] Seminary in 2001. I've been teaching and preaching since 1989.

I also have used kratom for the past 3 years. I had a bad accident that damaged both my skull/brain, spine and my pelvis about 15 years ago--I fell on the ice outside my home. As a result of the TBI and spinal cord injury, plus the pelvic damage, I was in terrible pain and prescribed opioids which gave me horrible side effects. I was also diagnosed with fibromyalgia and got sleep apnea through all this. I was no longer able to work as a full time pastor or substitute teach anymore as I had been. After finding a doctor who was able to help me, I started using kratom for the remaining pain that was not alleviated by therapy, and also used it as a direct means to get me off ALL the opioid medications the other doctors had prescribed. In one year I was back both in my pulpit, and now am finishing up my Masters in Special Education. I would not be teaching and working without having access to kratom.

Bottom line: Do my degrees and graduating with honors mean a thing if I can't go to work? Does having a family, a spouse who loves me and a home mean a thing if you can't enjoy it? I went back to coaching my son's baseball team. That wouldn't have happened without the kratom. I teach. I preach. I'm active. It's from being well for the first time in years that I am able to be a productive part of society.

Sincerely,
Reverend [redacted] [redacted], B.A., M.Div.

My name is [redacted] [redacted]. I am 48 years old, married with two grown children. I work in the mental health field and I have for almost 30 years. For many years I have had trouble with degenerative disk disease, arthritis and spinal stenosis. I took multiple analgesics for many years. I do not like the way that narcotics make me feel. I did a lot of reading trying to find alternatives. I became very ill 2 years ago and was diagnosed with multiple autoimmune illnesses. I have Lupus, Sjogren's Syndrome and celiac disease. The fatigue and body aches from autoimmune can only be understood by someone else with the disease. I had never found a way out of pain with prescription medications. I kept reading. There was a time when I took almost 30 pills a day between prescription medications, vitamins and supplements. I felt ridiculous taking these handfuls of pills. I went to doctor's appointments all the time. They were at a loss and I could tell that they were tired of me. I kept reading. I found out about kratom from another person with autoimmune. I tried it and have not looked back. All I have wanted for these past several years is to participate in life and function normally. This is the first time in many years that I have functioned like a normal person. I have not taken any of those prescriptions for months. I have also not cancelled any plans, haven't missed any work and haven't slept around the clock. I have never been high from kratom. I am not sure how I would even do that - never tried! I found a minimal dose to live my life and I have never been happier. I love life. I love my family, my dogs, my job, my friends and my community. I refuse to be a criminal so I don't know what I will do if I can no longer have kratom, I have not really thought about it because it seems so unreal to me. Please help us. Please don't ban kratom.

My name is [redacted]. I am 35 years old and married with two teenage boys. I have suffered from social anxiety, severe depression, and chronic pain for fifteen years. I've been prescribed many different types of medications for those disorders. All of the medications I've tried always caused me more problems than they solved. On prescription medications I was unable to work, and I couldn't take care of my family. Two years ago I found kratom. I've been taking kratom, one to two teaspoons in morning and at night when needed for two years. I am able to have quality relationships with my wife children and actually have

friends now. My social anxiety would not allow that before. I am more balanced and put together than I've ever been. I have been working in the same job now for two years, and was recently promoted.
My life was a terrible mess when I had to use Pharmaceuticals. I don't want to go back to that mess. Please don't ban kratom.

My name is [redacted] [redacted]. I am 35 years old. I found kratom 9 years ago and it saved me from a terrible addiction to opiate pain pills. I have many issues including insomnia, anxiety, depression, scoliosis, two slipped discs in my back, and a bad hip. Because of kratom I don't need any prescriptions. It helps me with all my ailments. I’m afraid of what will happen to me if kratom becomes a schedule 1. I will be forced back into my addiction with pills. This is life or death for me. Kratom is a miracle plant for me where no pill ever helped the way Kratom does. It's safe and effective with no side effects. Save our beloved plant.

My name is [redacted] [redacted]. I am only 32, and already medically retired from the Army. I take kratom for PTSD and OCD, after my doctor mentioned it. Before kratom, I was on over 17 different medications. All made my life worse. Caused me to become pre-diabetic, zoned out, worse mood swings, and didn't come close to touching anxiety enough to allow me to go to therapy. Now, with kratom, I am able to hold down a job as a veterinarian technician, and am able to be a part of my family. I can now make it to my daughter's recitals and games without being nervous or on edge. I can even talk in therapy without my anger and anxiety getting in the way. If kratom is taken from me, I will be taken away from my family. Either by the law taking me away because I refuse to stop taking kratom, or by death.

My name is [redacted] [redacted]. I am a 53-year-old mother of three and grandmother to one with one on the way! Before Kratom I was riddled with pain, had become reclusive, and didn't see much of a future. I was depressed, drugged and miserable having to endure the amount of pain I was in. Pain medications made my existence lonely and dependant. It just didn't seem like life was worth living with so much pain until a medical professional friend of mine suggested I try Kratom. Since taking Kratom, I no longer need pain medications (such as Percocet, Dilaudid, and tramadol), anti-anxiety medications, and anti-depression medications!! ALL GONE! My life has turned completely around and I feel alive again. I now feel I have a future to look forward to and can be the wife, mother, and grandmother I've always wanted to be. Kratom has taken away my pain, my anxiety and the depression resulting from so much pain. I have my life back! I'm healthy, clear headed, happy, and look forward to my future again! When I'm asked what will I do if the DEA succeeds? I can honestly say that I have only two choices to consider; continue taking Kratom illegally, or I go back on narcotics in full time pain management thereby ruining my life and the lives around me! THERE IS NO OPTION here! I don't want to die but I don't want a life on narcotics either!

My name is [redacted] [redacted], I am a responsible 50 year old man and use kratom every evening to treat my restless leg syndrome.I have been using Kratom for 2 years. Prior to using Kratom, I treated my RLS with Oxycodone and Tramadol. After 4 years I became tolerant and addicted to the oxycodone and Tramadol. Those medications were hurting me, not helping me. I found kratom online and used it to detox. It took away 90 percent of my withdrawals. I continued to use it every night for the last 2 years and it eliminates this horrible condition. If kratom is made illegal, I will die on the oxycodone again. Please don't make me go down that dark road again. I am happy and productive again and have no ill side effects from kratom. It has proven very safe and effective for me when all the other medications failed me. [redacted].

I am a 40 year old mother of 6. I was diagnosed with lupus, Sjögren's syndrome, fibromyalgia, hypothyroidism and chronic fatigue shortly after my twins were born in 2010. I spent 2 years trying medication after medication, looking for relief. The drugs I was put on caused a 70 pound weight gain in 2 months. The steroids made me blow up like a balloon. One of the medications was causing me to go blind. I couldn't lift my babies most days without crying out in pain. The fatigue kept me from playing and having fun with my children. I would lay in the floor and just cry some days because I was so miserable. I found out about kratom on a chronic pain forum and started researching. Within two months of trying it, I was weaning off the medications that were making me miserable. I was playing with my kids. I was cooking and cleaning and being the wife my husband deserved. My husband suffers from terrible disc degeneration. He is a mechanic and has to bend and twist all day long at his job. He tried kratom and he is now able to work through the day with minimal pain. Kratom has changed our lives and made us better parents. We aren't quite sure what we are going to do without it. - [redacted] [redacted]. Texas

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I am a 42 year old self-employed businessman. I have never been addicted to drugs or alcohol. I have however, suffered from anxiety and a herniated disc between my L4-L5 lumbar vertebrae. For years I had been taking prescribed Lexapro for my anxiety. When I started consuming Kratom, I was able to quit taking Lexapro. It was more effective and had no side effects. The biggest thing in which Kratom helped me with was my back. I was scheduled to have a microdiscectomy 1.5 years ago when I re-injured my disc. The pain I was experiencing was excruciating. I was prescribed high power pain killers which had horrible side effects, such as extreme fatigue, mental cloudiness, and upset my stomach. I decided to try Kratom instead and it was a miracle. The pain was severely reduced and there were no ill side effects. I was able to take Kratom in my work day and stay focused mentally without feeling tired. Because of Kratom I was able to take my doctor's advice and wait 4 month to see if the herniation would heal itself enough to avoid surgery...and because of Kratom, I was able to do exactly that! Keep Kratom Legal! -
[redacted] [redacted], [redacted] [redacted] FL

I am a responsible adult working as a General Manager at a restaurant, work 70+ hours a week and at the same company for 7 years and have been a part of the top 10% of my company for 2 of those years. I am a responsible user of Kratom, I use it for an energy boost for my long work shifts, as well as depression issues, and back pain. My life would be detrimental without it. I feel that if I am able to drink caffeine, alcohol, or smoke cigarettes, all of which are far more detrimental to my health and kill millions of people a year, I should be able to use this tea in my daily life without question. I feel the DEA has overstepped their bounds, and we should have checks and balances in place for them. They shouldn't be able to make federal laws without going through the public, or the other branches of government first. Not to mention this is a perfect way to start a black market for this product which would increase crime. Canada, Mexico, and the origin countries of this plant are all legal, which means easy entrance to the USA. I am not a criminal or an irresponsible drug addict, I am a hardworking American who takes care of his family any way possible. Please sign on to the letter, there will be millions of people suffering because of this.
[redacted] [redacted]. [redacted], Tx

I came to use kratom because I needed something that helped me focus on my schoolwork as well as help me reduce stress and relax on a daily basis. Kratom allows me to be more effective at school and I continue be more relaxed as I use kratom. Nothing else has been effective in my life to reduce stress or other anxiety issues without being on prescription medication. I prefer kratom because it is simple and doesn't have any negative effects on people. Kratom is safer than pharmaceutical drugs, with important medicinal uses and has changed my life.
[redacted] [redacted], NC

I am the mother of an incredible young woman who recently found Kratom and has been so much improved thanks to this wonderful plant. My daughter has been chronically ill since she was in elementary school. She was diagnosed with ulcerative colitis at that time. Since then, she's had many years of suffering through multiple surgeries and the side effects of having an autoimmune disease. To make matters worse, she has a permanent ileostomy, and eventually developed diabetes and arthritis. In spite of her illnesses, through the years she somehow managed to fight for a "normal life" with a husband and two beautiful children. But every year, the battle gets harder and she gets more tired and discouraged. For the last few years, the only thing that has kept her going was an Rx narcotic, but with the "war on prescription drugs" raging, she was one of the people who truly needed her meds, but was forced by the "pain management center" to be taken off the med that kept her functioning in the world. In desperation, she searched the internet for something that could help and found Kratom. She got immediate relief from pain, stress and insomnia by using this tea only a few times weekly. Just when things finally were looking up and she was able to get out of bed, cook for her family, go to her kid's school activities, etc., the DEA announces that they are going to put this TEA on the same list as dangerous drugs! I'm begging the reconsideration of the decision. Since hearing about Kratom (I was very skeptical) I have learned about many other people who are getting their lives back from chronic pain, insomnia, depression and many other terrible ailments without having to use narcotics or dangerous drugs. This is a miracle for many Americans, please, don't take it away.
Sincerely,
[redacted], Kentucky

I am a 36 year old male with a degree in Marine Biology that suffers from OCD, Depression, and ADD. I currently work as a lumber associate and thanks to Mitragyna, I am able to get through many painful days due to my conditions. I absolutely am for educating the public.
[redacted].[redacted]., [redacted] [redacted], FL

I am a mother that suffered from fibromyalgia and lupus but now that I found Kratom I am free of my pain and I could live a happy life.
[redacted] [redacted], TX

I am a 37 year old female and have dealt with severe social anxiety for all my life. After numerous highly addictive anxiety medication prescriptions, that did me far more harm than good, I researched herbal remedies for anxiety and came across Kratom. Kratom has saved me from a life controlled by severe anxiety that was so bad that at times I could not leave my house, work, or even drive. I am now a productive member of society. I am not an addict. I do not get "high." I do not even drink alcohol or smoke cigarettes. If this ban goes through, my life will return to a living hell.

I am a 57 year old male diagnosed with clinical depression and PTSD. Since discovering kratom 2 years ago, an occasional cup of kratom tea, approximately six times a week has dramatically reduced the anxiety/panic attacks associated with my PTSD. My doctor was very supportive. Because of kratom, I no longer have to take Xanax every four hours to keep the attacks at bay. The kratom also eliminated any withdrawal symptoms associated with the cessation of the Xanax. Furthermore, I find that I can go for several days to a week between consuming my kratom tea with no cravings. Truly a remarkable plant.

I have been on prescription pain meds for 15 years with little relief. I have fibromyalgia, lupus, osteoarthritis, rheumatoid arthritis, degenerative disc disease, and mixed connective tissue disease. I have suffered for years in pain and am currently on permanent disability at age 46. Within 2 days of

starting kratom (mostly red strains) I had no pain. I have not been pain free in 30 years! Kratom is my miracle.
[redacted] [redacted], NE

I'm 63 years old, a writer and retiree. I first learned about kratom online as I was searching for a legal alternative for chronic arthritis pain. My MD wouldn't prescribe the narcotic Vicodin even though I'd taken this medication for more than three years with no ill effect. The kratom I now use is called red vein Bali in capsule form. It doesn't make me "loopy" and has a mild stimulant effect like a good strong cup of coffee. What's more, my arthritis pain is hardly noticeable. I often go up stairs without having to hang on. With some changes in my diet I've lost about thirty pounds and while I wouldn't say kratom is an appetite suppressant it does seem to help me a little bit in that way. Like anything else it needs to be treated with respect and the potential for abuse is pretty small compared to a lot of other things.
[redacted] [redacted], CA

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am 50 years old and suffer with chronic Lyme disease. Before I started using kratom I wasn't able to hardly get out of bed. Kratom has given me the ability to live my life again. If it gets banned I don't know what I will do. I don't want to be on prescription drugs the rest of my life.
[redacted] [redacted], VA

I am a 48 yr old female who uses Kratom for severe menstrual cramps and PMS, and occasional back and neck pain. It works better than anything else. I have been prescribed opiates and they don't work and they make you feel fuzzy. I have been using it as needed for several years, I feel no addiction to it, coffee is more addicting. It's safe and it works. Kratom makes me functional and productive on days where with the pain, I would be non-functional and miserable.

I am a 45 yr old female from NC, who has been using Kratom responsibly for several years for severe depression & anxiety. I was finally able to stop taking my antidepressants, which were causing me ill side effects. - [redacted] [redacted].

I am a 36 year old female (mother of 4 and grandmother to 1) who has been responsibly using Kratom for 2 years. I use it for fibromyalgia, anxiety, acute gastritis, IBS and immunity. I take ½ teaspoon once a day, sometimes twice if it's really necessary. I've never upped my dose and I take regular breaks (one week a month and sometimes an entire month at a time) without experiencing withdrawal symptoms. My fibro is manageable, my anxiety, most of the time is under control, my acute gastritis attacks are basically null. I used to have these very painful attacks as often as several times a week or as little as once every couple months. Six ER visits in 20 years for attacks that were so severe, I feared something was horribly wrong. I've had only one gastritis attack in the last two years. I haven't been sick with so much as a cold in the last two years. The ONLY prescription I have is for ½ mg of Ativan for an emergency panic attack, and I might take that once every 3 or 4 months. The only side effects I experience with kratom are nausea if I take kratom on an empty stomach and don't eat within an hour, and constipation if I don't drink enough water. My biggest fear without kratom is going back to the painful digestive issues, and having to rely more on prescriptions to control my anxiety. I will never take a script for my fibro. I will also go back to spending less time out and about with my husband and children as kratom has helped me to the point where I can get back into the swing of things and not worry about the pain I might be in if I do this, or the anxiety I'll have if I do that. - [redacted] [redacted] PA.

I am a 33 year old female who has been using Kratom for approximately 2 years now. I have severe, chronic back pain that 12 doctors and specialists have been unable to diagnose. Through those 12

doctors, I have been prescribed every painkiller and muscle relaxant out there. None of them worked for too long, as I developed tolerances and the doctors would not alter the Rx. That sent me into awful withdrawal episodes that could last weeks. A friend recommended Kratom as a way to deal with the withdrawals. Not only did they help with that, but it completely ridded me of the back pain all those doctors can't figure out. I honestly cannot get out of bed and be a taxpaying, working member of society without Kratom.
[redacted] [redacted], MO

I am a 31-year-old graduate student, freelance writer, and psychotherapist. I've lived with chronic myofascial pain since I was 19. For the last four years, I have suffered from a severe and intractable iliopsoas spasm; when it flares up, it's so bad that I've cried myself to sleep and woken up screaming in pain. I used to be on a variety of prescription medications, none of which fully helped and nearly all of which interfered with my daily functioning. Almost five years ago, I began using kratom. Within months, I had phased out almost all prescription drugs. My pain management provider has marveled at the fact that I almost never need to take narcotic pain meds. In addition, kratom has helped me with depression and anxiety, as well as with seasonal allergies. Without kratom, I will almost certainly have to go back on prescription drugs. The quality of life that kratom has afforded me is immeasurable.
-[redacted] [redacted], Massachusetts

I am a 41 year old mother of 4 children. I have suffered from pain for 18 years. My pain is so severe that I feel like I am getting stabbed over and over again. A pain so intense that I feel like I am dying. I have endometriosis, arthritis and chronic kidney stones. I pass a stone once a month. Two years ago I found kratom and my life has changed forever. I am now able to function, I can now work, cook, clean and care for my 10 year old that suffers from type 1 diabetes. I am no longer bedridden, I am now happy. If kratom is banned, I fear for my future. A future of pain. I can not go back to that life of pain, I just can not. My life will be ruined if the ban goes through. - [redacted] [redacted] Colorado

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I am a 28 year old female that has been taking Kratom for going on 7 years. I suffered with horrible depression after the loss of my son [redacted], back pain, and recently found out I have Hidradenitis Skin Disease - for which there is no cure. My pain levels were so bad some days, I was unable to get out of bed. Now that I have found and take Kratom my depression is completely gone and my pain is under control. I am a Mom of 3 children and Kratom helps me be able to do all the normal everyday things! Kratom has gave me my life back and helps make each day easier. -[redacted] [redacted] [redacted],SC

I am housebound and mostly bedbound due to illness. I am immunocompromised and battling 12 systemic infections and have CFS. Kratom gives me a quality of life. I found Kratom while desperately seeking pain control in 2014. At the time I could not walk, I was 95lbs, and had no insurance. I began taking Kratom for pain that later had me in the hospital for 6 days. Once I got into a doctor, I was prescribed hydrocodone, tramadol, flexeril, oxycodone, dicyclomine, and buspar for pain and anxiety. I took these drugs for several months but the side effects were intense. I began to have rebound pain from the opiates and had to wean off. I used kratom to get through the physical withdrawal and then dropped those other medications as well. I have been using Kratom to control my pain ever since. -[redacted] [redacted], [redacted], KS

I am a 44 year old mother and homemaker. I have been ill for most of my adult life with Fibromyalgia, Chronic Fatigue and autoimmune like diseases with Neuropathy. Conditions that forced me to give up furthering my education after I earned a B.S. in Biology from the University of [redacted]. I have been on many allopathic medications. The majority of which, had such horrendous side effects that I could no

longer take them. Kratom has been a Godsend. It has helped increase my energy. It helps me get out of bed everyday and enables me to exercise more than I thought possible. Kratom reduces my pain and allows me to clean my house, and take care of myself and my family. I don't want to even think what my life will be like if Kratom is made a Schedule 1 drug. I had been on opiates for 5 years, when all the doctors began to stop filling prescriptions and pharmacies began to deny prescriptions. It is terrifying to be dependent on a medication that may be denied to you at any time for any reason. It is also terrifying to have to use medications that may cause your premature death. I was forced to quit working due to my pain and then I found Kratom. If it is taken away, I will have nowhere to turn. The frequently prescribed antidepressants given for my diagnosis have always given me side effects worse than my disease. I will not return to Western Medicine as it has not been a good fit for me. My pain is so great that at times I wonder how I am still alive. If Kratom is made illegal I will be relegated to a hellish life of constant severe chronic pain. This herbal has given me my life and hope back. Please do not take it away
- [redacted] [redacted] WY

I am a 34 year old father and husband and have suffered from severe food allergies. When I turned 28, I quickly discovered something was wrong as I was getting awful gastrointestinal distress, including diarrhea, gas and bloating when eating certain foods. I could not eat many of the major foods most people take for granted today, including dairy, gluten, beef, nuts, chocolate and bananas. I tried everything to cure my distress; from enzymes, to probiotics, to prescription medication as well as other natural remedies. Nothing worked. I spoke with multiple medical professionals, including a Naturopathic Doctor, nutritionists and dieticians. Nothing worked. My distress would become miserable and debilitating, and any little bit of dairy or wheat could set off my stomach. Many days I was spent bent over and curled up in the fetal position due to extreme gas and bloating. Many hours I spent suffering on the toilet with no relief. I could not live a normal life. The proteins my body was sensitive to, were in almost everything. My quality of life had been severely degraded. So I began to scour the internet and do my own research to look for something that could relieve the issues I suffered from. After some time researching, I stumbled up Kratom. People with colitis and other intestinal diseases said that Kratom took the edge off, both pain wise, and intestinally. So I gave it a shot. From the moment I started using Kratom, I was able to eat whatever I wanted with almost no ill-effect. I have been taking Kratom successfully for 3 years. I do not know what I would do if Kratom became illegal and I was unable to use it. I know my quality of life would degrade severely. I know I would have to go back to reading every single ingredient in everything I bought. I know I would not be able to eat nearly anything that is served at a restaurant. My job and career depend on me taking customers to lunch or dinner at restaurants. This would be a severe hit to me and my family as our food bill would increase due to having to use substitutes. I hope the DEA or other government entity would reconsider making Kratom Schedule 1 or my life and my families life will forever change for the worse. - [redacted] [redacted]

I am a 27-year-old honors student, single mother, and community volunteer. I suffer with Ankylosing spondylitis, fibromyalgia, and PTSD. Before I started taking kratom, I was considering dropping out of college and applying for disability assistance because I no longer could tolerate the pain and side effects of my many medications. I was becoming depressed as I could not be physically active with my daughter. I found kratom while asking other chronic illness patients for suggestions on alternative, natural supplements. Kratom helped ease the joint stiffness, muscle spasms, and panic attacks I was constantly experiencing. I completed last semester with a 4.0 GPA, won a prestigious scholarship, and felt well enough to mentor at-risk youth. I also now do yoga, participate in an honors society at school, and enjoy outdoor activities with my daughter. I have never experienced adverse side effects from kratom, and I have been able to stop taking muscle relaxers, narcotic pain medication, and antidepressants. My quality of life has drastically improved because of kratom, and there will be dire consequences if I can no longer use it as part of my health and wellness routine. [redacted] [redacted], [redacted], NC

I am a 55 year old mother of 4 and grandmother of 6. I was a legal assistant/ paralegal for years for a large law firm. In 1995 I fell and hurt my back and had back surgery. I later, in 2006 had a large deep vein thrombosis in my left leg, from my groin to my foot. I now have permanent nerve damage and neuropathy. I was on methadone through pain management for 6 years. I tried the blocks, a neuro-stimulator , physical therapies and of course the methadone. I lived my life in a constant fog, unable to care for myself or my daughter. I stopped taking methadone in 2010 and just suffered. I spent most of my time in bed, avoiding family functions because the pain was so severe. I looked into natural pain relief and found Kratom. I have been using Kratom now for about 7 months. I function and find myself able to do more things ,such as buying my own groceries due to the pain relief. I am able to think clearly and enjoy my grandkids (I missed so much time with them). Kratom gave me my life back. I love my life now. The thought of losing something natural, an herb, that is safe and effective scares me. What will my choices be then? Am I doomed to a life of severe pain, or opiates that slowly take my life away? Do I go back to just existing because it hurts to bad to live? - [redacted] [redacted] Kentucky

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I'm 35 years old. I started using kratom after many failed prescription medications and jail visits. At 18, I was prescribed oxytocin, then later Xanax, Wellbutrin, Zoloft, Methadone, Klonopin, Adderall, and Suboxone. I couldn't stay clean or keep a job. I was always relying on the state for food stamps and welfare to provide for my kids. Today I've been clean 3 years and I have a full-time job. I don't rely on the state for anything. If kratom is banned I could die or be a felon!!! Thanks [redacted]

When I was 17 years old my mother was shot and killed by my stepfather in the front yard of my house. I witnessed everything. I tried to kill him before he drove off to his apartment to later commit suicide. I witnessed my mother's death at an age where my brain was in need of maturing. I developed severe PTSD. My senior year of high school was mostly sleeping through classes and getting involved with the wrong crowd. Before this, I was a great student and never missed a day of school. At one point the PTSD was so bad I wouldn't come out of the bathroom after a shower due the fact that I thought someone was waiting to kill me on the other side of the door. I would wait for hours and cry. Completely turned my family away and shut them out of my life. I ran off to college to escape everyone I knew. I turned to drugs to get away from the severe depression and anxiety from the PTSD. My life was a train wreck for about 8 years. I found Kratom and sobered up. I don't drink but once every 2 months thanks to kratom. I'm happy to say that I consider myself sober thanks to this plant. It has truly saved my life and helped me from killing myself. I finally have my life back and am happy for the first time in 9 years. I turn 27 in december, and I have a positive outlook on my life for the first time in years. I work out 5 days a week and am in the best shape of my life. To add to my wonderful life i have an amazing 3 year old son. If you want more details, feel free to message me. I am scared for my life for this ban. I CANNOT go back to my old life without a fight. I truly and honestly witnessed hell at such a young age. I would not wish this card of life on anyone, not even my worst enemies. I beg you to reconsider for my life, my son's future, and so many others lives.
- [redacted] [redacted]

I'm 55 years old. I'm gainfully employed, a homeowner, a grandmother, a National Merit Scholar (way back in my school days). I'm the farthest thing from a drug addict, but prescription painkillers nearly made me one. I had an accident a few years ago and was very slow to heal. Before I realized it, I'd been taking the Vicodin my doctor prescribed for 4 months and I'd become entirely too fond of it. I started researching for a way to give up the painkillers but still manage the pain. I opted to try kratom and it did just what I needed it to. It got me off the pain pills and back to a healthy and productive work & social life. Kratom is now my go-to when I need pain treatment, because I don't ever want to tempt fate with prescription painkillers again. I also have a family member who prefers it to the Prozac that he'd been taking for 20+ years. Kratom provides him with anti-anxiety benefits without the unpleasant side-effects of the pills. I would hate to see a safe and natural alternative to dangerous opiates and chemical mood enhancers taken away by this ill-advised scheduling -[redacted] [redacted]

I'm 44 years old. When I was about 22, I was diagnosed with depression, OCD and Anxiety Disorders. The doctor put me on 20 mg of Prozac and over the years has increased the dosage to 60 mg. But over the years, I realized it wasn't working well anymore, because those feelings of anxiety were coming back and I couldn't shake them off. About 4 years ago, I decided to try kratom for my mood disorders and it works so much better. I don't have to take the Prozac anymore and I don't have the undesirable side-effects from the prescription drug. I've lost close to 50 excess pounds, because I'm much more alert and active on kratom. I used to come home and sleep for 15 hours a day. Now I sleep about 6 to 8 hours, like normal people do. Not to get too personal, but the Prozac also had a negative effect on my sex drive and my wife is much happier now that I've found a better anti-anxiety treatment. I've been taking kratom daily for over 4 years now. It doesn't get me high – it makes me feel like a normal human being again. I get things done and my judgment doesn't get clouded by anxiety and paranoia like it used to. Please do not ban kratom – I don't want to have to go back to a less effective choice with unpleasant side-effects. -- [redacted] [redacted].

My name is [redacted] [redacted] [redacted]. I'm a 41 year old stay at home mom to a 4 year old boy. I have suffered for many years from late stage Lyme disease, which is notoriously difficult to treat. My symptoms include deep fatigue and a lot of varied pain, among many others. Kratom has been more useful to manage my pain and fatigue than any other pharmaceutical or herbal remedy I have tried. I have been taking it regularly for well over a year with no signs of building up a tolerance, or any other negative side effect apart from some occasional thirst or constipation which is easily managed. Kratom truly has become instrumental and indispensable to me being able to lead a semblance of a normal life while fighting this insidious disease. If it were banned, not only would I personally suffer, but it would also strongly impact the kind of mother I can be to my son, and wife to my husband. - [redacted] [redacted] [redacted], [redacted] CA

I'm a 56 yr old wife, mother, mother of an angel (my [redacted], age 11 1/2, to CF in 2000), grandmother, and former PI (specialties: Reuniting families and assisting in the search for the missing, primarily children) who was forced to retire too soon due to; Chronic Migraine (15+/mo), Pancreatitis, IBS, Fibromyalgia and more recently, MS. I am unable to take any type of OTC or prescribed pain medications; my system simply treats them as poison and I wind up admitted to the hospital w/migraine, uncontrolled projectile vomiting and life threatening extremely low blood pressure. For the past 15 years, I have dealt with the extreme pain of my various illnesses myself, w/no meds, which caused even more health issues, extremely high blood pressure and depression amongst them.

I honestly didn't realize how much pain I was in on a daily basis, until I tried Kratom and within minutes, 80% of the pain disappeared. In addition, I was not dizzy, "high", buzzed - none of that. All I felt other than the lessening of pain, was total relief. It's been a year now and Kratom continues to be a God-send. I am not addicted to it, take when needed, and with this miracle, have begun to take up the dropped reins of my life. The migraines are not completely eased, but all other painful symptoms are, and I am now advocating for the missing again; reuniting families again. Kratom has helped hundreds of thousands of folks, with pain, and to recover from addiction. To ban this natural miracle would cause us all including myself, to return to a dark life full of pain. I cannot even imagine how that will be possible, to return to my housebound, bedridden pain-filled self. I just can't. I just cannot comprehend how we're expected to do that. How are we to explain to our families and children who are so thrilled to have the old "us" back? How? - Kind Regards, [redacted] [redacted], [redacted] [redacted], MO

I am a fifty-six year old woman who has been partially disabled and in pain for most of my life, due to scoliosis and lordosis, two kinds of spinal curvature. I now also suffer from debilitating arthritis, fibromyalgia, sciatica, migraine and pain-related sleep disorder. The herb kratom helps enormously with all of these conditions. Pharmaceutical medications do not address these illnesses sufficiently. Without the herb kratom I would be mostly immobile, unable to do the limited work I can now do. I wouldn't be able to contribute to our local economy as I do now. I might not be able to live independently, as I do now. The pharmaceutical medications that I'd likely be prescribed are very addictive and also very harmful to the body. This is widely documented. Forced to rely only on prescription medication, I would be dealing with issues associated with those medications on top of my illnesses, resulting in decreased well being overall. Because of a lack of independence and decreased well being and health, I would likely suffer depression, necessitating treatment for that issue also. Pharmaceutical treatments for depression have their own very serious risks, also widely documented. Basically, I see a future of needless suffering & a downward spiral if the herb kratom is banned. I have been using kratom for two years. The sense that I have the power to determine my own health is extremely important to my well being also. ~ [redacted] [redacted]., N.Y.

I'm a 32 year old responsible woman who is also a single mother to two little boys. I have a B.A. In Psychology and am a domestic abuse survivor. I've been using Kratom responsibly for the past 6-9 months as a supplement to my Dr. Prescribed medications for Narcolepsy... I was diagnosed in May 2015. I have depended on stimulant medication prescribed by my doctor (in doses well above the FDA recommendations) for the better part of 6 years now. I have also depended on anxiety medications (benzos) to combat the anxiety that the stimulants were giving me. I have tried every single stimulant on the market and almost every single antidepressant on the market. The stimulants came with a lot of side effects and I hated how up and down they make you feel. Nothing was ever consistent and I was always tired. It was a disaster. The pharmaceutical drugs helped minimally but did not get me anywhere near being a functional member of society (let alone a mommy). I haven't been able to work for the past 2 years thanks to my condition. My ex husband's child support, food stamps and parents have been my only source of income for quite a while now. When I started looking into Kratom I was at a point physically where I didn't think pharmaceuticals could help me much more, so I needed another option. Narcolepsy can quite literally destroy your life and body, and at my worst I was sleeping 18-20 hours a day... I could not accept that as my reality because of my two children. I did all my research and decided to give Kratom a try- crossing my fingers it would help me.

Kratom in low amounts is stimulating and so I found that just a very small amount (1-2 teaspoons) a few times a day helped me tremendously. Not only did it decrease my extreme daytime fatigue, it almost completely eliminated my anxiety. When I first started using Kratom I had no idea just how much it would change my life- not only was I able to stop taking Anxiety medications (benzos) I was also able to stop taking stimulants. 1 teaspoon of Kratom three times a day did more for me than 120mg of Adderall and 3mg of Ativan. I am feeling better than I have in a really long time and Kratom is a really big part of the reason why. My health is completely consistent and because of that, life is soo much easier. I've been thinking about getting a part time job in the next 2-3 months. I will not be able to do that if Kratom becomes a schedule 1. Honestly, I fear for what my life will go back to if I am no longer able to use Kratom. I love being healthy and I'm going to be honest- I'm very upset that this is happening. What did I do to deserve this? I'm just a single mother trying to raise my babies in my small town, and I got a stupid thing called Narcolepsy. I fought like hell to get better and to where I am now, life without Kratom will be terrible.

My life with no Kratom will be one I never thought I would have to go back to. When I have gone 30 days without it, I will be back to relying on just prescription medications to manage the symptoms of Narcolepsy. Adderall and Ativan, because there is nothing more helpful than Adderall and with that comes a lot of anxiety as a side effect. I will be ok one day and not the next, and when I say not ok I mean I'm literally not able to wake up and function outside of my bed. Within a month I will become tolerant to the Adderall and will have zero good days anymore. I will most likely have to get in touch with my doctor and have her switch me to a different stimulant in the hopes that it works. It won't, I've been through this cycle many times. I will have no option but to deal with the fatigue and will not be able to look for part time work like I was anticipating doing in the next few months.

This ban will not only impact me, it will impact my children as well. They have long forgotten the Mommy who was always too tired to play with them, cook for them and enjoy life with them. I will lose so much more than just energy as I will not be able to spend nearly as much time with them due to sleeping all day. They deserve to have me at my best to take them to school, cook healthy meals for them, teach them how to play soccer- all things I can do now, but will not be able to do after September 30. It breaks my heart for them, for me, and for everyone else who will be affected by this scheduling. It is unnecessary and not fair- and I hope the people responsible for this know how much they are hurting people like me- you're hurting my children too.

My name is [redacted] and I am a mother of 4 children. I work in the medical field in a high up position. I am involved in my kids school and after school activities. I run a non-profit group for kids with cancer. I have never been an alcoholic or misused drugs. I googled something natural for anxiety and came across this plant. All those things listed above, I wasn't able to do for a few years due to horrible anxiety. I wasn't able to handle the social interaction. I could barely make a phone call. Now I am back out in the world. My anxiety is under control for the first time in years and I am afraid of going backwards. This plant has changed my life for the better.

My name is [redacted]. I am a 42 yr old chronic pain patient. Before I found Kratom I had become totally bedridden and dependent on prescription pain meds. After suffering horrible withdrawals, I vowed never to go back to pills but the pain was too much for me to handle. I eventually attempted suicide to end the unbearable physical pain. When I was released from the psych ward, I started looking for a natural way to relieve my pain and heard about kratom. Kratom has given me my life back. I am no longer bedridden. I can enjoy playing with my son and granddaughter. I no longer want to die but I am frightened. I am afraid that if kratom is taken from me, I will not be strong enough. I am worried that it will push me back to the pills or even worse. I cannot handle going through withdrawal again. I JUST CAN'T. If I do not go back to those horrible pills, I fear that I may once again become suicidal. And next time I may not be so lucky. I am literally afraid for my life.

My name is [redacted] [redacted]. I have suffered from endometriosis since I was 14 years old. Endometriosis is a chronic, incurable condition that causes intense pain on an intermittent basis. When I was 21, I underwent surgery to remove the endometrial adhesions, but the adhesions quickly returned, which is extremely common. I tried a variety of medications to manage the condition, including NSAIDs, but by the time I was 25, my doctor told me that my only remaining options were to take opioid painkillers or undergo a hysterectomy. Everything changed when I learned about kratom. Kratom helps to ease the endometriosis "flare-ups" without the use of opiate painkillers. I have been using Kratom for several years with no ill effects. It has helped me tremendously with my symptoms, allowing me to be an engaged wife, mother, and contributing member of my community. My health has never been better. Without kratom, I will be forced to use opiate pain medications or undergo a hysterectomy at the age of 34. I am hoping for an opportunity to have a second child, and I am not exaggerating at all when I say that kratom is what is preserving my fertility. -- [redacted] [redacted], Age 34, [redacted], WA

I am a 32 year old stay at home parent. I take care of my one year old and I am fostering my seven year old nephew who has complex medical conditions. I have been taking Kratom for over 6 months for my fibromyalgia, back pain and endometriosis. I was able to get off my prescribed narcotic medication thanks to Kratom. Kratom helps manage my daily pain, mood and gives me energy that I have been lacking for years. Kratom makes me feel normal, unlike the narcotics that made me feel like a zombie. I can only hope that this plant stays legal, so I can continue giving 110% to my family and live a drug free and clear headed life.

I am a 38-year-old single mother of two with fibromyalgia and kratom has been a GODSEND in my life. Kratom makes me feel well and energetic again. It relieves my pain and gives a boost to my mood. My children need me and I am scared to death that the ban will leave me exhausted, in pain and unable to work or care for them.

I’m a 34 year old Ohio native and I used kratom to get off of heroin. Full stop. No suboxone, no methadone, just plain leaf Kratom and a bed. I found that it also helped with my anxiety, so I asked my doctor to taper me off of Klonopin. Kratom is also a wonderful antidepressant and I’ve asked my doctor to lower my dose of Effexor. She was doubtful and didn’t want to do it, but she did, and I’m in better shape than ever. Once this scheduling happens, I honestly don’t know what’s going to happen to me.

I am 57 and have been nearly bedridden for 12 years due to a wreck that has left me with a severe case of occipital neuralgia. Nothing, including narcotics, has given me any consistent relief until now. I just found Kratom about 6 weeks ago and the difference has been amazing with no side effects. Please don’t take away the life I have just been able to start living again. [redacted] [redacted], [redacted] Oklahoma.

I'm a 42 year old female with several health problems which cause chronic pain. Kratom has by far exceeded previous contemporary treatments and medications. Before this DEA intent was filed, I believed that with the help of kratom I would quite possibly be able to work again. Now my life is on hold again. I'm terrified of the possibility that I may not only lose 'my miracle', but that should I need to go back into pain management, I may not even have access to my previous medicines due to the sweeping changes made in the few months since I voluntarily left. What particular type of evil is in play when one is persecuted for trying to make healthier, safer, more responsible choices? I'm at a loss to understand this. - [redacted].[redacted]. ID

My name is [redacted] [redacted]. I'm a 41 year old woman who lives with CRPS, the most painful disease known to man, Multiple Sclerosis, and Fibromyalgia. For 16+ years I've dealt with debilitating chronic pain, depression, and anxiety as a result. I've tried almost every therapy and medication offered to me over the years, with very little positive effects. The pain was very poorly controlled and the depression had me in a place emotionally, that I was suicidal. I saw myself as nothing but a burden to the people around me and the world as a whole. I heard about Kratom in a social media group for chronic pain. I researched, and with the blessing of my doctors, who all felt it was a safer alternative to the opiates and narcotics I'd been reliant on to that point, I gave it a chance. 11 months later I have found some pain relief and find that it's enough to allow me to be an active participant in the world around me, as opposed to a sobbing lump on the sofa or in bed. I am able to do basic household chores again, and to get out into the world for short periods. Things that weren’t possible before kratom. I literally fear for my life without the help of this herb. - [redacted][redacted][redacted]

I'm a college student studying computer science and I've long been a musician, which has kept my hands and arms extremely busy for most of my waking hours. During my senior year of high school I started to notice pain creeping up in my arms and this grew to be debilitating. I was made to choose between completing my school work or practicing my french horn enough to be ready for my weekly lesson (I attended an arts school so much playing was demanded of me). I took measures to reduce performance anxiety so I wouldn't be squeezing the instrument unnecessarily intensely which helped a bit, but the pain didn't cease entirely. Going to a doctor was unattractive to me as I don't trust myself to handle messing with opioid medications, and turning to NSAIDs actually ended up giving me a stomach ulcer after using ibuprofen daily for a long time period. Finally during my freshman year of college I was introduced to kratom at a local kava bar and found that it helped immensely with my symptoms. Ever since, I've used it on days when my arms are in high demand and I no longer had to worry about putting myself in immense pain just to maintain basic function in my life. I've never been anywhere close to addicted to kratom, and from what I understand it has many pharmacological targets not shared with traditional opioids that may mediate its more mild dependence liability (antiglutamatergic activity, specifically, unless I'm not remembering correctly). So now with the DEA's knee-jerk banning of kratom, the only two medicinal herbs I know of that helped me with my symptoms are deemed to have "no accepted medical use" and attempting to use them will deem me a serious criminal to polite society.

I am [redacted] [redacted] age 44. I took Kratom to get away from Opiates. Kratom helped address the four things that always made me relapse; depression, anxiety, fatigue and pain. Kratom brought me back from the brink. I would likely have overdosed, died or been thrown in jail if not for kratom. I know that I am not the only one for which this is true. If kratom is taken away, I can't say what would happen. I would lose my drive to live and be a better person. I will be sorely tempted every day to give in and give up. God knows what will happen. I can only hope that the DEA or congress will see how kratom has saved my life and not make me a criminal. This is all too real. This is my life. I don't want to be a criminal, relapse or die. Please don't take away what allowed me to be a productive member of society after I just got my life back in order. Please don't do this to so many people. We want to live normal lives within just laws of society. This ban is a grave and a destructive tragedy.

My name is [redacted] [redacted], 44, father of one, and I am a disabled professional with 15 years of print production experience for large fortune 500 companies. I got injured in 1990 and was in a car accident in 2011 that brought my previous injury to the breaking point. After 2 major back surgeries and the loss of my job, I am waiting for my Social Security hearing (29 months to date) and have no health insurance. I have been taking Kratom for pain (about 2 years), and have no way to get any other medicines. Kratom helps me to feel a little better, and if the DEA pushes this ban through, I will lose access to the only pain control I have. If this ban goes through, I am horrified at the pain I will again feel. Kratom allows me to move around the house and to do simple things in my everyday life, that others take for granted. Kratom allows me a little relief I cannot get elsewhere. Thank you - [redacted]

My name is [redacted] [redacted] and I am a 54 year old female. 20 plus years ago I was in an auto accident. I had a lot of soft tissue damage. Since the accident I have been diagnosed with more than 20 diagnoses. Everything from Fibromyalgia to occipital neuralgia. My life became one of pain at the moment of impact. I was told for the first 6 months I would get better, but I didn't, I got worse. I am intolerant to most (almost all) pain medications. I made a number of attempts to take them but they just made me too sick. I then tried every therapy possible. I started getting trigger point injections and cervical epidural injections, but they just never did anything positive for me (although I went in for dozens of these out of desperation). I even considered having my nerves burned until I was told the risks and the possibility that the pain would get a whole lot worse before it MIGHT get better (and the fact that the nerves could come back so to speak). In the last 2 years I have had to have 4 surgeries, 2 on my right knee and one on each shoulder. I made it exactly one day for 3 of the surgeries on pain meds before I switched to Kratom.(The last surgery, I was on pain meds a lot longer than I thought I would be due to surgery failure. I questioned the entire time if the vomiting induced by the medications was worth it and decided no, and switched back to Kratom 2 weeks later. The pain from the last surgery continues to this day but I only use Kratom for it). I simply cannot tolerate opiates or even the synthetics (Tramadol). Kratom has given me my life back better than anything else ever could. I still have days that are not so good, but I am no longer lying there waiting impatiently for death. Now I find myself living in fear (and my family has fears as well) that come the end of September I will have to stop the Kratom due to DEA's decision. I feel like I have 11 days at the time of this writing for relief and then I am not sure what is going to happen. KRATOM SAVES LIVES! Please save so many of us from a possible horrendous fate and keep this plant legal and accessible.

My name is [redacted] [redacted] from Massachusetts. I am 46 years old. I lost my daughter, [redacted], to this opioid epidemic, over one year ago. She got addicted to oxycontin that was flooding the streets before anyone was knowledgeable of the dangers. I never had a chance to warn her. She battled until she was 28. If I knew then what I know now about kratom, I'm confident she would still be here. I now use kratom for the emotional pain I will have for the rest of my life. I have been using kratom for about 9 months. I use it all day long. It gets me through each day without feeling so lost. I get no side effects, and I use a lot. I'm distraught at the thought of not having this wonderful, god-given plant for my pain.

My name is [redacted] [redacted]. I am 37 years old, I work as a customer service manager, I am a mother of four, a wife, a daughter, and soon to be grandmother. Two years ago I was on the verge of losing my job due to poor attendance because of the pain and fatigue associated with ehlers-danlos syndrome, fibromyalgia, and neuropathy. The pain would keep me in bed for days unable to function. I joined a couple facebook support groups, because i was to the point that I prayed to go to sleep and not wake up. Someone had shared an article on kratom, so I did a lot of research and listened to a lot of testimony. I decided to try it, because i had already tried everything else. Two years later, I am back to working full time, and am no longer at any risk of losing my job. I carry my own medical insurance, and pay my own medical bills. My quality of life has improved to where I enjoy waking up and facing each new day. To take away something mild without side effects is inhumane. We are adults who have a right to choose what we put into our bodies. My frame of mind greatly improved after tapering off of the prescriptions that had such harsh side effects. How is this a bad thing? If they make kratom a schedule 1, it will confirm my belief that the government doesn't care about the people anymore, that all they care about is money. Let us live our lives in peace, in the land of the free that America was supposed to stand for.

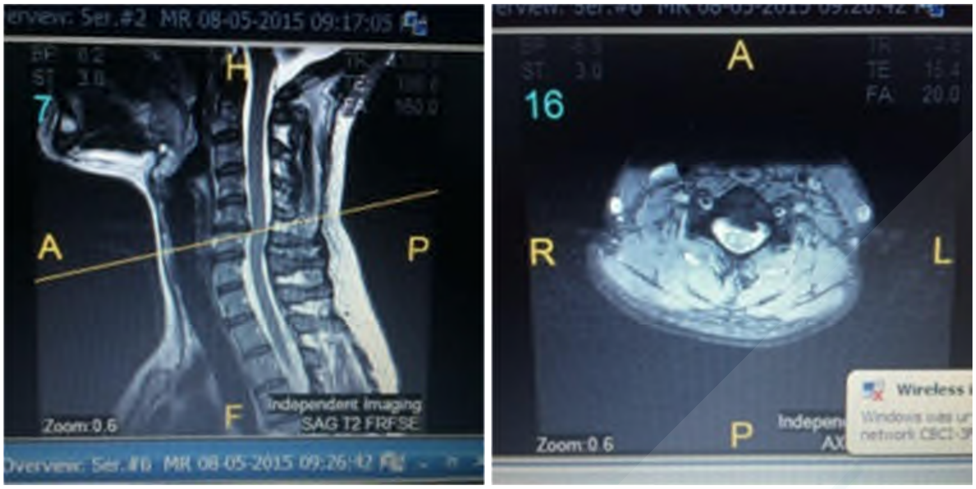
My name is [redacted] [redacted]. I am a 34 year old Innovation and Experience Designer specializing in the research and development of natural gestures for human-computer interfaces in cognitive systems engineering. I have been sick for 25 years with invisible illnesses and autoimmune conditions. So somehow I've managed to grow up with crippling symptoms and yet manage to succeed. But lately my symptoms have degenerated to the point of disability. On good days, I can shuffle-walk. I can barely sit up and have a conversation. I can chew. On bad days, my eyes swell shut, my fever confines me to lying down, I'm nauseated and have no strength to walk or sit up, and intense burning neuropathy pours like hot lava throughout my back. Many people with invisible illnesses suffer in silence. Our doctors call us liars; they say it's "something the mind makes up to get attention"; they tell us our problems are weight-gain/loss related while refusing to believe that the weight issues are the result—not the cause—of our pain and fatigue. I was a child the first time a specialist, I had traveled 3 hours to see, told me to "stop making up the symptoms." I was a preteen struggling to breathe when a pain specialist accused me of coming to him "just for narcotics." Very recently, I finally discovered the source for all my autoimmune responses—Lyme Disease and co-infections. These bacterial infections have burrowed deep into my joints, my organs, my bone tissue, even my brain—into crevices where white blood cells have no access, far beyond the reach of antibiotics, even where palliative pain medications give me no comfort. Like all late-stage autoimmune Lyme patients, the treatments I undergo are experimental, cutting edge, involving new medical technology at the forefront of a poorly understood disease. I travel far to seek treatments. And in order to do so, I require at least some relief from symptoms to give me the sleep and the energy I need to do what is necessary for my treatments. I have never taken narcotics in my life; I have never taken nor been addicted to opiates. Yet I take Kratom because it gives me long lasting pain relief from symptoms that are otherwise entirely crippling, without the nauseating and dizzying side effects I get from prescription pain drugs. I have never felt it to have any addictive hold over me; when I don't need it, I don't need it and that is a surprising and wonderful feeling. But when I do, I most certainly do. It is not a cure; but it is the only thing that allows me to get to my doctor appointments, to sleep without painful tremors, to meet with Lyme specialists, and to aid me in my journey for a cure. If you take away this means for pain relief, you are making it impossible for me to seek the care and treatments I need. If you seek to regulate it, then do so without scheduling it in the same category as heroin, and do it in a way that lets those of us in legitimate pain access it as the tool that it is, a medicine.

I am a 50yr old mother and grandma that suffers from chronic pain. Diagnosed with several ailments, my lower back is what puts me down on a daily basis. The pain takes away my sleep and has me tossing and turning most nights which led to depression. It was awful until I found kratom 3+ years ago. My daughters introduced me to this natural plant that has since changed my life. I can sleep. I can move around more easily. I laugh and smile again. What was once a bitter woman that people hated to be around, because I was miserable, has turned into a friendly, happy, caring, loving person that has become a great mother and grandmother. Kratom has gave me life back. I use it daily to help reduce pain and lift my mood.

I feel if kratom is banned, it will send me back into the doctor's office trying to get painkillers. I feel like my life as I know it, will change back to where I once was. Depressed, in pain, miserable, sleepless and hopeless. I don't want to become a criminal for using a plant that is illegal. I need kratom in my life daily. I've tried other plants and most medicines made today, and none of them work for me. I love that kratom gave me a freedom of choice. I don't have doctors degrading me, thinking it's all about the drugs when it wasn't. It was, and always has been about the pain relief. Kratom helps with that. It's given me so much more than I ever thought possible. My dignity, self esteem, worth, happiness, joy, family, friends, all came back to me. Please don't take it away.

I am a 44 year old mother of a college student. I work in the corporate world and am a Vice President of Sales for a successful software company, have a successful career, and I am college educated. I pay my taxes. I have never been arrested. I have never even had a speeding ticket. I don't drink much and I don't do recreational drugs. I grew up with parents who did believe that conventional medicine is a last resort to use only when natural medicine has failed or is not helpful enough. We drank a lot of yucky herbs and learned to take horse pill sized vitamins at a very young age.

About 7 years ago I was in an auto accident, where I suffered two herniated discs and several torn muscles. Since then, additional discs have herniated at random due to gravity. One of the discs is literally pressing 20% into my spinal cord. Doctors and Chiropractors alike recommend surgery (I don't trust the neck surgeries, as I have seen too many failed). The last Osteopath (about a year and a half ago) I saw couldn't believe I was even functioning and immediately prescribed me a bottle of Percocet. I still have them, and hold them for emergencies. He said that if I didn't want surgery now, that he would gladly send me to pain management. My regular doctor will prescribe Vicodin if I ask, because my pain and ailment is quite well documented. The drugs are not hard to get when you have proof of pain like mine. Here are two pictures that are MRI's of MY NECK:



The 2nd picture is a top down view. The white spot in the middle is my spinal cord. The dark part protruding into it is my disc, stuck into my spinal cord. This is what pain looks like on film. What it feels like is a constant pinch in my neck, that runs down to my upper trapezius and down the back of my shoulder. At times when inflammation is present, the pain can go all the way down my arm and even make me lose all feeling, except for pain and numbness in my fingertips. My right hand has permanent weakness, and this is documented by both doctors and chiropractors. This injury means that I can't open a jar or do anything that requires hand strength. Besides a college degree, I also have a massage therapy license. I do not practice any longer because I am not able.

I do have chronic pain. I do have in my possession, Percocet. The same bottle the Osteopath prescribed over a year ago. In the past year, I have taken 3 of them. The year the accident occurred, I spent about two weeks taking full doses of Vicodin every day. I started to feel a craving for them as they exited my system. I knew about Kratom, but had only tried it once. Someone suggested I try it for pain. To my surprise, it worked and that's why I don't use the Percocet.

I drink one or two cups of Kratom tea daily (most days). I have been for several years. Sometimes I travel for work and don't have it for several days. It does not bother me. I don't seem to have any form of withdrawal. I make the tea at home from leaf purchased on the internet. I drink it in the afternoon, when sitting in the chair at my desk has started to wear on my neck and shoulders. It enables me to keep working with a clear mind and reduces my pain. If I am still in pain at the end of the day, I have a second cup. Never has my boss or coworkers asked if I am messed up, on drugs or thought I was not ok. I function completely normally with Kratom. The pain is reduced enough that I can continue working and remain productive. I can even do gentle yoga a few times a week. Without it, I would need to resort to the Percocets that I keep in my purse for fear of having a bad pain episode. I don't know what I would do if the Kratom ban goes through. Live in pain? Live with a foggy mind and end up losing my job due to real drugs and what they call "pain management?" Those are the only options available, neither of which I want.

I have annual check ups from my doctor. All of my blood work is normal, everything shows that I am a healthy individual. If you want to see copies, I will send them to you. Kratom has not harmed my organs, my cholesterol is perfect, my vitamin levels are also perfect. All is well! Please don't take it away! I'm so scared to have to make a choice between constant pain and losing my mind on hard, dangerous Opioid drugs. If Kratom is banned, will the DEA compensate me in salary, since the ban may cost me my job? Sincerely, [redacted] [redacted], [redacted] FL

I am a 42 year old mother of 2 suffering from bulging and torn disc at L4 and L5. I suffer from chronic pain daily as a result. I spent 7 years allowing a doctor to prescribe me opiates as the answer. My breaking point was when I came down with the flu and couldn't keep anything down including my meds. Sadly my body had become addicted to the medication and I was hospitalized as a result of the withdrawal. That was my breaking point in deciding I would not allow my body to be controlled by a pharmaceutical. I found Kratom and it provided more relief than I ever had taking the morphine. I no longer have to worry about being addicted to a medication and I can once again function and participate with my family. Taking Kratom away will leave me no choice but to return to pharmaceuticals to ease my pain. This world has enough of an opiate problem without adding me as another victim to that number.

About two years ago I was going through a very difficult period in my life. My wife and I had separated, and not long after, the resulting depression that set in started to take a toll on my work and my personal life. My doctor put me on antidepressants. Within a few weeks things got better. My wife returned and my work and personal life improved. About a year later though, something happened. The medications stopped working. Literally just STOPPED. It was like a light switch had been turned off. My doctor and I tried different dosages and medications but none of them worked. However, because of the dosage changes, my body and mind started going through withdrawal symptoms. I don't know if you've ever experienced these symptoms, but I pray you haven't and that you NEVER have to go through them. One of the symptoms can only be described as a "brain zap". It's literally the feeling of an electric current going through your head. Every few seconds...zap...zap...zap. Couple that with migraines, inability to sleep, and mood swings like you wouldn't believe. There was only one drug that mitigated the symptoms. I found that Tramadol stopped the brain zaps which allowed me to sleep which allowed me to regain my strength and keep everything under control. Then.the FDA/DEA reclassified Tramadol. My doctor couldn't prescribe it to me. I started to spiral down again, but then a miracle happened. A friend of mine suggested I try an herbal remedy called Kratom. I did some quick research and decided to go for it. I was looking for any relief. My order arrived a few days later from a company in Austin. I can't adequately put into words what happened other than to say it was a GOD SEND. A TRUE MIRACLE FROM HEAVEN. I found relief within 20 minutes. In fact, not ONLY did the brain zaps stop, but over the next few days and weeks, I found it had an analgesic effect on my back and provided me with an energy boost.

I have been using kratom now for a little over a year and it's helped me get my life back. I'm no longer on antidepressants or any kind of pain medication for my back. I have energy again and I no longer have the mood swings that plagued me for so long.

Please help me and countless others. - [redacted] [redacted] [redacted] [redacted], TX

I am a 51 year old male from [redacted] [redacted] Florida. I was prescribed narcotic pain medication in 2001 for degenerative spine injuries from working full-time as a plumber since 1980. Two of my lower disc in my spine are squished out from the front of my spine and they are in-operable. I currently still work 70 hours a week. Narcotic pain medication which consists of an opiate, worked for the first few months of the 15 years. It started off with a simple prescription. A decade later I was on the strongest dose allowable, taking a synthetic opiate called Methadone eight times a day the highest milligram tablet. With this narcotic pain medication, I had to get prescription opiates of different types for breakthrough pain. Those prescriptions lead to asthma and I needed prescriptions for that. All of the above led to prescriptions for depression. At the end of the decade I was taking six prescriptions costing $800 a month. My health was so poor I was only working 10 hours a week. On the verge of losing my business and all I owned, my son introduced me to KRATOM. Within months I stopped taking all of the prescriptions and within two days I was not taking Methadone and only KRATOM tea. Five years later I only make a cup of tea for my chronic pain. This plant which is in the coffee family has no tolerance build up and no dependency. I cannot go back to taking pharmaceutical opiates or any synthesized drug. Today I am free from side effects from the prescriptions I used to take, and I feel like I am 19 years old again, back to working 70 hours. If you ban this plant which you do not have any constitutional right to do so according to the 9th and 10th amendment you will see tens of thousands of people die from drug overdose and suicides and crime to pay for prescriptions they can't afford. No one has ever died from taking KRATOM ! You already know this. Stop working for big Pharma. The research you did to get this ban, you surely realized that Kratom is the only remedy for many illnesses and had no side effects. Do the right thing and lift the ban because thirty days after its banned, those who had to stop using pharmaceutical prescriptions, which is everybody who's using this plant, will get very active and boisterous about government corruption and relationships that should not exist between bureaucrats and corporations. We don't need anymore problems with trust in government and we don't need any of nature's plants banned. You don't have the right or the authority to ban a plant!

I am a 56 year old grandma raising 2 grandchildren. 13 years ago I was struck head on by a drunk driver. Prior to that I was a hospital technician and on my way to finally getting my RN license. Since that day I have been a chronic pain sufferer. 13 surgeries, hip replacement, MRSA, 2 ankle replacements still pending, fibromyalgia, and hypothyroidism. I have been on pain meds with all their nasty side effects since. The pain doesn't go away. My doc's answer is to prescribe more. Prescribe stronger meds. More side effects, less living. I found Kratom through a website for fibro pain sufferers,did some research and very hesitantly ordered some. Luckily I found a wonderful vender and to my surprise Kratom worked. It helped with my pain, depression, and anxiety. Because believe me when you are a chronic pain sufferer, depression and anxiety are both part of it! Kratom does not take away all of my pain.but makes it livable.It improves my attitude and makes me look forward to life again. There is no high from Kratom. If there was, I would not use it. I have used it for months and then stopped with no problems.This plant has helped so many. Regulate, please do not ban. - [redacted] [redacted] [redacted] Arkansas

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My name is [redacted] [redacted], and I am a 41 year old woman with mild cerebral palsy (from brain injury at birth), and an autoimmune disorder which is on the Lupus spectrum. I am married, work in construction management and am a professional musician and photographer. Kratom helps me manage my chronic pain and fatigue symptoms. Before Kratom, I took a number of painkillers and muscle relaxants, but they left me very groggy and dizzy. I also developed gastritis from the overuse of painkillers, so I had to stop. It was difficult to be fully functional at work, at home and socially. I felt as though I was in too much pain to be engaged with the world. I became increasingly depressed and withdrawn. But fortunately, a friend introduced me to Kratom. It is a supplement that eased my chronic pain and fatigue to a level where I can now be more active and involved. It has made a tremendous difference in my life. I recently started going to the gym to make my body even stronger now that the pain has been lifted enough for me to do physical activity. I have increased my work hours and my outlook on life has brightened. I am much happier and healthier overall. Please do not ban this supplement that allows me, and so many people like me, to function in a fuller, more productive way. - [redacted] [redacted] [redacted] [redacted], FL

My name is [redacted] and I have been using kratom for four years now for a lot of reasons. Ptsd ,bipolar depression,restless limb,and back pain. This plant has helped so many people for so many different reasons. I was able to stop taking a few of my prescription meds when i started taking kratom. I still take a few but not as many. People addicted to heroin and various pain meds are able to use this harmless plant to get free of their addiction. Thousands and thousands of lives will be negatively affected by this ban.

I am a 42 year old man with a wife and 2 sons. I have a bachelor's degree and work as a network engineer. I'm a musician and artist. In 2002 I was suffering with chronic back pain. It was so bad that I couldn't exercise and it affected my work life where I spent large parts of my day sitting. I gained 60lbs and was eventually diagnosed with a degenerative disc disease and sent to a spine specialist. They gave me narcotic pain killers. A LOT of them. They helped the pain but made me groggy, drowsy, constipated, etc. I was never an addict but I was headed that way when I found kratom. After starting kratom I was off of all narcotic pain killers. I was able to get back to soccer and lost 70 lbs. I started coaching soccer for my kids and volunteering to help kids w special needs play soccer. I wasn't groggy or drowsy at work and in the 5 years I've been using kratom, I've had no side-effects. Stopping it suddenly will cause me some fatigue and an upset stomach. Hardly anything compared to stopping narcotics. If this ban goes through I will be faced with either suffering in pain daily or going back to doctors who are reluctant and judgemental about prescribing narcotic painkillers. I have a lot to lose if kratom is made illegal. Taking narcotic painkillers makes you feel euphoric. Taking more than you should gets you high. Kratom does not make a person high.

My name is [redacted] and I am a 34 year old married women and a mom of two little boys. I have an MBA degree but I currently have decided to stay at home with my kids. I am also a person who has greatly struggled with depression and anxiety, and chronic debilitating tmj pain. Those issues resulted in me drinking a lot, and I became a very dangerous alcoholic. According to the doctor back then I was ruining my liver, I was also ruining my life. I could not hold relationships and felt totally isolated. Thank God I quit drinking before I had the kids. Alcohol is truly the most dangerous drug out there, legal or not. It kills more than the opiate epidemic does each year. The fact that I can walk right next door to get deadly alcohol makes me scared, If they succeed in banning Kratom. Kratom has helped me remain sober for almost six years now. It helps greatly with my depression and anxiety so that I was happy again and could form relationships and got married. It also helps tremendously with my severe tmj. I was supposed to have surgery over 20 years ago but my dad didn't want to pay for it, so now my teeth don't fit together and my jaw hurts so bad I don't like to talk or eat. Kratom has also helped me greatly with that pain. I can now live my life in less emotional and physical pain. It is also imperative that I stay off alcohol, because it will probably kill me if I drank again. I am a great wife and mom now. I am a productive member of society, and I even work out everyday. Kratom greatly helps my quality of life in many ways. If it is taken away from me all the problems stated above will come back to me because I definitely can not go back on those pharmaceuticals that were dangerous and put me in a fog. I have family that needs me so this ban will affect them negatively as well.

My name is [redacted] and I am a 39-year-old mother and computer science student. This wonderful leaf has helped me greatly. I sometimes have small amounts in a tea and it really helps with my treatment-resistant depression and anxiety as well as pain. I have a history of extreme trauma and have developed PTSD from many negative life experiences such as severe peer bullying, child abuse, the murder of my father and other unfortunate events. I've tried many pharmaceuticals since I was a teen, and I developed a terrible alcohol problem while trying to get some relief from my unbearable feelings of sadness and fear. Thanks to Kratom, I am 18 months sober from alcohol. Kratom helps not only my physical pain, but my mental pain, and the lack of motivation that causes a cycle of more depression and immobility. I can't go back to that life. It is not living at all. I want to be a productive member of society, I want to be a good mother, and I want to be law-abiding. Please do not make me a criminal. I am not a bad person, I am not looking to get high, I am just in pain.

I am a 27 year old male student who has been in the workforce since I was 15. I have no arrests, traffic tickets, or criminal history whatsoever in my life including as a juvenile. I was a 4.0 student and member of my high school Key Club where I logged 100+ hours volunteering. I have been employed full time in the construction industry, as a retail sales manager, and as a solar installer. I own multiple houses and have clear titles on all of them. I am self taught in two foreign languages which I speak with high degrees of fluency. I aspire to continue my college education and ultimately work in the healthcare industry as an ARNP or MD.

I am a diagnosed bipolar with an anxiety disorder. I use kratom as a supplement for my depressive symptoms and anxiety as a substitute for prescribed drugs such as xanax, valproate, valium, and lamictal. If this ban takes place I will be faced with a barrage of prescription medications with a myriad of potentially dangerous side effects to manage my condition. The prescription medications I will be required to take are highly addictive and also make me feel 'high' which causes me issues with concentration, work performance, and academic pursuits. With access to kratom, I brew a tea which I drink twice daily and have no issues or need for prescription medications and their side effects. - [redacted]. [redacted], [redacted], Florida

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My name is [redacted] and I'm 52 years old. I've been a chronic pain sufferer since the first car accident in 2004. My first pain relief was hydrocodone. I was also injured in a 2nd car accident in 2007 one year after the spinal fusion to repair the damage from the first. I was also physically assaulted in 2009 which threw all the rehabilitation out the window and began my journey in Dilaudid, Morphine and Percocets. I've never abused these drugs but was treated as such. The medical community began pulling the rug and tapering me very quickly due to the heroin overdose epidemic. I was led to Kratom which as been a God send. If the DEA take this away the ONLY choice will be suicide as I've decided I will not live the rest of my life in agony. - [redacted]. [redacted]. Rochester, NY

My name is [redacted] [redacted] and I am a mother of three, with an undergrad degree in Finance and Masters in Education. I have used kratom tea over the past year, after searching for herbal remedies for my mild anxiety. I also run half marathons, and running has proved to be an outlet for stress relief as well. Kratom tea has also helped manage pain with injuries that I have sustained from running, including five knee surgeries to date. I also use other herbal supplements and plants to treat ailments. I feel as though the Government, in particular the DEA, is taking away my rights to live a healthy and happy life. Why do they get to choose what I put in my body if it is causing no harm to others or myself? I feel healthier and happier than I did a year ago. I have never felt "addicted" to this plant or felt as though it was dangerous in any way. I will continue to fight for this freedom, for myself and others, and because I want my children to learn that you fight for what is right. If the ban takes place, I will be forced to find an alternative to aid in managing my anxiety, and most likely it will be more harmful and less effective. I pray the DEA does the right thing, and pursues regulation over prohibition. - [redacted] [redacted], 34 [redacted], PA

For ten years, I have suffered with the consequences of Lupus, which include chronic pain, sleep issues, stress, and fatigue. Medical professionals prescribed several types of medications for these issues including barbiturates, benzodiazepines, hypnotics, muscle relaxants, SSRIs, and strongly suggested I try opiates for pain management. At this encouragement, I sought healthier alternatives. The interactions and side effects from these drugs required constant experimentation, new prescriptions to counter adverse effects, and general discomfort. With a condition as unreasonable as lupus, stability and health become precious resources.

In 2015, I researched Kratom as an alternative. Luckily it has been able to replace the unstable drug regimens strongly suggested and provided reliable results and stability in treatment. It allows me to take several less pills with highly undesirable side effects and varying effects, pills not safe for long term use which is necessary from chronic health conditions. The DEA Kratom ban will upend my effort to manage my chronic symptoms safely. Rather than put my health in a further precarious state, I am inclined continue to live internationally to avoid federal prison for my healthcare needs. Kratom mitigates the majority of these extraneous lupus issues while providing consistent energy. - [redacted] [redacted] [redacted], TN (Currently, international resident). Age 28

My name is [redacted] [redacted] and I am a Senior Software Engineer. I have Chronic Fatigue, Fibromyalgia and multiple spinal disorders. I used to be on Vicodin, Gabapentin and other prescription medications for pain management. Kratom helps me manage my pain and fatigue without any need for other medications. Unlike prescription pain medications, kratom allows me to have mental clarity so that I am able and keep my full time job as a software engineer. If kratom is made illegal I will have no choice but to go back to the prescription opioids that aren't as effective and have side effects that affect my logical thinking and make my chronic fatigue worse. I will loose my job because opioids impair my ability to think. Also, due to my constant debilitating pain, I am at risk for opiate overdose.

Kratom has helped me cope with pain, severe fatigue, and anxiety due to chronic illness, including fibromyalgia. I'm [redacted] [redacted], a 52-year-old mother of two teenagers. I'm no slouch: I've earned a Ph.D. and two master's degrees at Stanford and Cornell. I work as a professor. I was high school valedictorian. I won a host of prestigious scholarships and awards. But illness doesn't spare the high achievers of the world. When I got sick in 2008, and stayed sick, I could barely function.

Several months ago, I tried kratom. I'm a scholar and a skeptic, but I decided it was worth a try. Kratom changed my life. My pain has become far more manageable, and I've regained the energy I need. Yet my mind is clear enough to teach complicated at the university level. The "psychoactive" effects of kratom are limited to a mild mood boost; they don't make me stupid, interfere with reflexes, or otherwise impair me. I no longer fear that I will have to retire early, and I'm able to resume volunteering in my community. My life has become richly meaningful, thanks to my renewed ability to be of service. Not least: I smile and laugh more, and I'm more available to my teenaged boys. I have hope that I can live, not just exist – all thanks to a plant that is closely related to my morning cup of coffee.

My name is [redacted] [redacted]. I discovered Kratom over a year ago. I am a resident of Alabama and have been very afraid of what the government will do to me. I was a responsible user of Kratom, I have an Associates Degree in Medical Assisting. I have been working in the private sector for over 20 years. With all the tugging and pulling and moving of patients I developed degenerative disc disease, L5 disc is completely destroyed and a crack in my spine right above it. When Alabama decided they knew better what I needed than I did, I did the only thing i could, I suffer. Once in awhile we go out of state just so I can have relief for the weekend or a couple day, otherwise I suffer through it. I will never put my family or home in jeopardy having it here, but it has hurt my ability to work like I used too. I had the ability to make over $700 a week working while I was taking Kratom. Now I barely can get up to move and make $100 a week. We are in jeopardy of losing our home, (which is a tiny house) that we built ourselves from a shell of a storage building and our vehicles, we are dependent on my husbands income alone now because the State of Alabama chose to ban this plant that absolutely helped me in every way. I am praying this ban does not go through and it will help get Kratom back in Alabama so it can again let me be able to go back to work full time and be the person I once was while taking it.

My name is [redacted] [redacted]. I am a 44 year old Catholic School teacher and the Director of Technology for the largest parish in [redacted], NY. I live in [redacted], NY. I was diagnosed with degenerative disk disease and spinal stenosis in 2000. I was 28 years old and was offered either oxycontin or spinal surgery. With one option I would have become dependant on opiates for life, or go the other route, and risk paralysis. I chose neither, so I chose to suffer. For 11 years I used Advil and Aleve. Advil did liver damage and Aleve caused wicked bleeding ulcers. I gained 100 lbs. I found Kratom through a Google search, for "natural pain relief" and tons of Kratom articles and success stories came up. I read, I researched, I purchased. On December 16, 2011, the chronic pain in my back was eliminated within a half hour of drinking my first cup of Kratom tea. Since then I became active, focused and motivated. I hit the gym again, and I lost the 100 pounds plus more. I am the healthiest I've ever been with a very physically demanding job.

If Kratom were to become illegal, I would be forced to stop it. Considering I am refusing synthetic pills and surgery, and I refuse to break the law, I guess I will end up on disability by the time I turn 45. I'm sure the weight will begin to add on, and I will eventually become homebound. On the days I don't use Kratom, my pain comes back with a vengeance and it would be impossible to continue my career. As of now, I am a healthy productive teacher. Please do not ban Kratom. I do not deserve to suffer for the next 30-40 years. It will destroy my family. I'd lose my home because I would not be able to afford my mortgage. I would lose everything. I refuse to take chemicals. I deserve to choose what I want to put in my body. Thank you for listening.

My name is [redacted] [redacted], I'm a 39 yr old wife and mother to 4. I have fought severe scoliosis since I was 13 and was diagnosed with Fibromyalgia, major depressive disorder, neuropathy and CFS to name a few. I was on meds for 10 yrs including narcotics, and was sleeping my life and my kids life away and was a zombie. I was looking for natural remedies and came across Kratom, I ordered some and never looked back!! In 3 years Kratom has given me my life back. I'm finally able to work after not working for 10 yrs, can run and play with my kids and have my life back!! Please keep Kratom legal and don't take my life away!!

[redacted] [redacted], age 57. Medical pain management for spinal, hip and knee pain from an accident when I was 13 years old. Before and after recent surgery I was on prescription opiates for several months which were absolutely debilitating and habit forming. Since I started drinking an occasional cup of Kratom tea I haven't touched opiates. If Kratom is banned I will have no choice but to go back to opiates.

My name is [redacted]. As many others have, I found relief from several ailments using kratom. Ever since I found kratom, my quality of life has went up drastically. I am a 27 year-old who suffers from severe anxiety, depression, and chronic pain, and found solace shortly after discovering kratom 4 years ago. While my legal prescriptions to pharmaceutical SSRIs, painkillers and anxiety medications have somewhat helped, all of them concluded to actual danger to my health and mental state, along with harmful side effects. They did not compare to the safety of using the kratom tea to ease chronic pain, depression, and anxiety. This natural remedy is certainly the optimal solution in this case, as many others have found. I have since been able to rebuild my life, get off harmful prescription medications, and have once again become a positive member to society. The inability to use kratom would certainly regress my lifestyle and do real harm to my well-being. I could not imagine having to go back to a life without kratom.

My name is [redacted] [redacted]. I was diagnosed with generalized anxiety disorder, RLS and related pain in 2012. I have been prescribed benzodiazepines, SSRI drugs and muscle relaxers. I am currently taking none of those horrible medications. Before my diagnosis I abused alcohol to sleep and deal with the anxiety. Honestly, while I was not anxious and could sleep on these substances, they stole my life. I was depressed, uninterested in anything that gave me joy and stalled out in my Doctoral program. Kratom has replaced all of these dangerous and addictive substances. It is a miracle herb and has given me my life back. I am currently working in Kazakhstan as an Assistant Professor of Media and Communication. I would have not been able to do this without Kratom. I have my Ph.D. and a variety of publications in my field. I do not feel addicted and have gone without the herb for extended periods of time. These periods are miserable not because of any withdrawals, but because my symptoms return.

I am sad to report that living here in Kazakhstan, I now feel more free than if I were in the United States. Also, I will not be able to return because I am about to be turned into a criminal. If I do return, then I will either be forced to submit unwillingly to medical treatment that I do not find productive or I will be forced to break the law in order to treat myself as I see fit. This is undue burden--forced to choose between something bad (dangerous medications) and something worse (jail) based on a unilateral decision made by regulatory agencies without any legislation or proof. The Alabama disaster will be repeated, with a 20% spike in overdoses and thousands of new opiate and benzo prescriptions issued. These drugs are the health threat, and this legislation will criminalize those of us avoiding this threat. Kratom is invaluable and it is of great importance to those of us who want to have options beyond what is peddled by big pharmaceutical companies. - [redacted] [redacted], Ph.D. [redacted], Kazakhstan & [redacted], Tennessee

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My name is [redacted] [redacted], I'm a 48-year old teacher, mom and grandmother from Oklahoma. I heard about Kratom through an on-line pain support group. I suffer from Depression, Neuropathy, severe anxiety, Sjogren's Syndrome, fibromyalgia and arthritis. I have tried every prescription drug available. I was taking so much medication, I had to take medication, to deal with side effects of medication. I still had so much pain and the same symptoms I had begun with. Nothing worked. I have been dealing with my conditions for over 20 years. Before kratom, I was beginning the process to get on disability. I had no hope and no life. After kratom, I can work, play with my grandchildren, go for a walk and be a contributing member of society. I still have pain and anxiety every day but it is a lot less with kratom. If kratom is taken away I will be on disability, not able to work, not able to play with my grandchildren and I won't have any hope. I don't want addictive pain medicine that makes me feel high and that have other horrible side effects. Kratom is a plant that doesn't have horrible side effects and doesn't make you high. If kratom is taken from me I will wish I were dead because the pain will be so great. I don't want to go back there to that darkness of constant pain. I thought I lived in America where we were free to choose a plant to help our health if we wanted to??

I'm a 61-year old mother of three sons & one daughter-all of whom I have raised to be caring, law-abiding, hardworking, productive citizens of this great country. I have a beautiful 2-year old granddaughter & a grandson on the way. I have a great accounting job at a small company. Thanks to kratom, I rarely, if ever miss a day of work and I'm able to play with my grandchild, take her for walks to the park, and care for her 2 days a week. You see, I also suffer from debilitating knee pain along with severe neck pain from an injury. I use kratom leaf for my pain. I take about 1 teaspoon in the morning & another one at night. It's not a miracle cure, but it works very well for my pain and allows me to live my life fully and give myself to the people I love. I have been using this wonderful plant for a little over a year now. It never leaves me feeling "drugged" like I felt on pain medication. I never need more than my 1 teaspoon and I never crave more. I've never robbed a convenience store to get it and no one has ever found me passed out in my vehicle because of it! I just had my annual physical and I'm in great health. My husband and I bicycle often, sometimes 40 miles on a Saturday. I couldn't do that without kratom. I really believe this plant has helped me get my life back. To ban it not only makes NO sense, it's absolutely ludicrous. Turning many thousands of decent, good & law-abiding people--the many grandmas, grandpas, veterans, thousands of women suffering from endometriosis, & countless others who use this herb to improve their quality of life--into felons is a sad commentary on how low our misguided war on drugs has sunk. Not to mention the hypocrisy of banning a plant that helps so many people get off of the dangerous drugs that this very war is about!! - [redacted] [redacted], [redacted], MN

I'm a 47 yr old high school teacher and mother of two. I've always been really active on my own and with my kids. As years went by my fatigue and widespread pain got worse until I barely got out of bed. I was diagnosed with osteoarthritis, psoriatic arthritis, and Fibromyalgia. All of this on top of the IBS, displaced cervical discs, degenerated discs, TMJ Disorder, and migraines that I had been being diagnosed with since the 8th grade. We tried the Cymbalta, Lyrica, and gabapentin (Norco for only the worst of days). With each, I got worse instead of better. Within six months I had packed on 60lbs and could barely function through the basic necessities of daily living. I seriously gave thought to removing myself from this planet. I ran across someone who told me about Kratom for pain and fatigue. I researched it and eventually gave it a try. I was amazed at the pain relief, energy boost, anxiety relief, and mood boost that it gave me. I used it to take myself off of one pharmaceutical at a time. It took months and the withdrawals from Cymbalta, Lyrica, and Gabapentin were horrid. The only pharmaceuticals that I still use are Enbrel injections, muscle relaxers, and the very rare Norco. Kratom has given me my life back. I'm a functioning interactive mom and high school teacher again. I gain no "euphoria" or "high" with Kratom. There's no intellectual muddiness, like with opiates or the antidepressants previously prescribed. The only side effect, if I take too much, is nausea. I switch strains each dose to keep my tolerance low, at 3-6 grams. I take it only when I have to, in order to be able to move. I still feel pain 24/7 but it's tolerable most days and I gladly smile again. We MUST keep Kratom legal so that I can keep my life. - [redacted] [redacted] Texas

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I'm a 31 year old mother of three. We homeschool and have a small homestead. Kratom is an awesome supplement that really helps with my chronic pain caused by spinal problems. I've been diagnosed with DDD, scoliosis, spondylosis, arthrosis, a fused SI joint, a bulging disc, torn spinal tendons, myositis, fibromyalgia and carpal tunnel. I've been taking kratom for two years now with no adverse effects. It helps with both my pain and the depression caused by chronic pain. I've never gotten any type of high from kratom and I've never had any of the side effects that go along with opioid use such as dizziness, nausea, confusion or respiratory depression. I would much rather use kratom to help my pain and depression than take lots of pills that affect your mood and ability to function. God gave us plants to help with the problems that arrive in life and I would be greatly disappointed if it was taken away. Many people use kratom to help with chronic pain, anxiety, depression, ptsd, etc. Not one death has ever been attributed to kratom alone and it isn't a danger to anyone, even in high doses. It doesn't cause dependency, side effects or any kind of altered state of mind. Please don't take away this herb that is so helpful to so many. Thousands of people have successfully used kratom to permanently stop taking prescription opioids or using street drugs. I would say with today's opioid and street drug abuse epidemic kratom would be very helpful in preventing further overdose when used to wean off of other drugs. It doesn't treat or cure any illnesses but can certainly help with the symptoms of pain, depression or withdrawal. Please don't take it away from us! - [redacted] [redacted], Texas

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My name is [redacted] and I am 45 years old! I suffer from chronic pain due to DDD, herniated and bulging discs in my neck with bone spurs, dehydrated bulging discs in my lower back with a fracture, fibro, migraines, severe nerve root lesions, and crippling sciatica! When faced with all of this pain I am not able to perform my daily tasks, I end up bedridden for days at a time, and this causes depression! I have been to Pain Mngmnt and I ended up addicted and abusing the meds! I went to the methadone clinic and I ended up addicted and abusing that also! I stopped it all cold turkey and thought I would die! I began drinking heavily to numb the pain! In December 2015 I was introduced to Kratom and there has been no looking back! I have no desire or need for pills or alcohol! My quality of life has improved 110% with Kratom! Just when I seen the light at the end of the tunnel I feel like the rug is being jerked out from under my feet! PLEASE do not take this plant away and force me back to pharmaceuticals and/or alcohol! It will ruin everything that I have worked so hard to repair in my life! - [redacted] [redacted] [redacted], Ga.

I am 50 years old and use Kratom to ease the pain and fatigue of rheumatoid arthritis and neuropathy. Before Kratom I could barely get through my work week and I would just sleep through the weekends. Since I have been using Kratom I am thriving at work, still have energy after work to exercise and enjoy activities on the weekends. I even earned a Master's Degree because I finally had the energy I needed to study after work and on weekends - [redacted] [redacted] [redacted]@[redacted].com [redacted]-[redacted]-[redacted]

My name is [redacted], I'm a 43-year old male from Wyoming. In 2009 I suffered an injury at work. I have a herniated disc in my neck that causes me daily headaches, problems with my vision, painful muscle spasms in my neck, head, back, and shoulder. For 6 years I took harsh and addictive prescription painkillers and muscle relaxers. This year I was fortunate enough to find kratom. I have not had one sick day from work since starting to take kratom.

I can't imagine going back to life without kratom. The thought makes me tearful and scared. Please don't take kratom away from me! My professional career and home life will suffer again for sure!
[redacted] from Wyoming

[redacted] [redacted], 30, [redacted] [redacted], TX

I first learned of Kratom in 2013. I was an alcoholic and in a very difficult time in my life. I literally used Kratom to end my addiction to alcohol over several months. It provided immediate relief from my cravings and put me in a state where I was more motivated to focus on doing things positive for myself. I have continued using it regularly to this day, on a daily basis. In 2015 I suffered a back and leg injury that caused chronic inflammation and pain. I had no health insurance. To this day I still maintain a highly active and productive lifestyle thanks to this natural compound. I can manage my pain and stay in a great positive mood at my 60+ hour/week job with no prescription medications or abuse of any other substances like alcohol. Kratom has changed my life literally. I have recommended it to friends and family, some who have adopted it in their lives with great enthusiasm. For me, Kratom is primarily a safe and highly effective pain reliever and aid for any all forms of fatigue.

My name is [redacted]. I am a 34 years old. My husband and I have been married 11 years and we have a 9 year old son. My husband is one of the most amazing people I have ever met. He holds multiple advanced degrees in Physics, Education, and Engineering. He plays 5 instruments, writes music and poetry, has a black belt in Jujitsu, builds furniture, blows glass, makes pottery, loves camping and hiking, and can fix my car. Seven years ago he began suffering from muscle spasms and debilitating migraines. After several MRIs, the doctors found that due to sports injuries sustained as a teen, my husband’s shoulder blade and upper spine are wrapped in a mass of scar tissue that can not be operated on. He spent the next 3 years in physical therapy, having injections, and prescribed every painkiller, muscle relaxer and pill his doctors thought might help. Although the medications alleviated pain, they left him just a shadow of his former self. He could not work or participate in activities he enjoyed because his medications made him disoriented and dazed. He became depressed, slept most of the day, lost interest in family, and we ended up in marriage counseling. However 4 years ago a family friend suggested my husband try Kratom and it literally changed our lives. Today along with Kratom, he is prescribed only one medication to prevent migraines and one muscle relaxer that he takes occasionally if he has muscle spasms from too much physical activity. He no longer has to have injections or physical therapy. He works full-time, has been able to return to his hobbies, and even coaches our son’s little-league team. Kratom gave my husband his life back and in turn gave me back my husband and my son his father.

My name is [redacted] [redacted] and I am 35 years old and live in [redacted], Oregon. I am a [redacted] [redacted] [redacted] at the Department of Human Services. I have used kratom for Restless Legs Syndrome and Irritable Bowel Syndrome since 2008. Before finding kratom I tried every prescription drug that is on the market for both of my chronic conditions. Every single medicine I tried was ineffective, or the side effects were so bad I was unable to continue treatment. In fact, the anti-Parkinson's medication my doctor prescribed for my Restless Legs Syndrome actually made my symptoms worse (this is a common side effect called "augmentation").

I am a law-abiding citizen (I had to pass a background check to be employed at my current job), and I respect the law greatly, and one of the main reasons I chose kratom (like the hundreds of other people I have talked to in the kratom community), is because it is LEGAL, and because it does not alter who I am as a person like some of the medications I used to take for my chronic health conditions. It does not impair me, alter my thinking or behavior, or affect my judgment.

The DEA may think it's as simple as choosing not to use kratom anymore if the ban goes into effect. But I have two serious chronic illnesses that have been successfully managed with kratom for more than 8 years now. I can sleep at night and not crash my car when I'm driving because an RLS flare up happens all of a sudden, because my RLS is helped greatly by kratom. I can focus at work because my RLS symptoms are under control. I can not wake up every morning sick to my stomach and throw up every day before I go to work, because my Irritable Bowel Syndrome disappears completely when I take kratom.

What does the DEA expect us to do? They have put us between a rock and a hard place. Most kratom users respect the law like I do, and are not criminals. We don't abuse illegal drugs, most of us don't even drink alcohol or use other prescription drugs. We are moral, ethical people by and large. But we also have chronic illnesses that require treatment, and kratom is the only thing we have found that works. It has given us our lives back. That is why you will find such passion among us. We are literally fighting for our lives.

I am a 54 yr old wife, mother of 4 and grandma to 3. Raised in an abusive home, I went on to an abusive relationship that lasted 4 very long years. I have suffered 31 breaks, including multiple facial trauma, cervical & spinal fractures, seizures, tremors, was in a coma for 9 days from a beating and hospitalized for several days from being stabbed repeatedly. As a result, I had migraines that could not be treated successfully, nerve damage that affects my arms and hands which forced me to leave my job as a hair stylist, was diagnosed with fibro, CFS, a\r. Fifteen years ago I was rear ended by a large van and pushed into oncoming traffic that put me in therapy for over a year, I never re-gained all my movement or strength and added to my chronic pain. I went from Dr to Dr, to several specialists and each told me there was no hope for recovery and all they could do was try to manage my pain. I have been on Fentanyl, oxycontin, Methotrexate, percocet, percodine, codeine, Tylenol 3, Flexeral, Antivert, Dilantin, Cymbalta, Lyrica and others plus multiple shots of cortizone, steroids and nerve blocks in an effort to relieve my pain. None of them really worked; they either left me sleepy, unable to concentrate, feeling “out of myself” or just plain made me sick. To add insult to injury, I also found myself on other Rxs to combat the side effects of high blood pressure, nausea, IBS, body rash, mouth blisters, blurry vision and more caused by the Rxs meant to help. Then, about 4 years ago I found kratom. To be honest, I didn’t expect much but I did want to get off ALL the meds or at least as many as possible. Kratom has changed my life; all by itself. I am clean of any Rx drugs and rely solely on Kratom now and even though I am not 100% pain free, I am 100% chemical free and that alone thrills me. The best part of Kratom is that I control my dosage, how much and when I take it and it is affordable--even though it is not covered by insurance. If Kratom becomes illegal, my life is over. I am happy now, I can sleep almost through the night; most nights anyway and even though I still have to space out my activities, at least now I can still consider going places. Before Kratom, I felt like a home bound prisoner. Please do not take away my only lifeline to family, friends and a future.

My name is [redacted] [redacted]. I am a 48 year old mom of 6. I used to work in a RCFE and in schools as well as at the juvenile hall! I suffered Herniated discs in lumbar and cervical spine! I also was diagnosed with carpal tunnel syndrome and had the surgery to release the nerves in both hands as well as a rotator cuff surgery. I am unable to do the work I used to do and when taking prescription opioids I developed high blood pressure and other unwanted side effects. Kratom has made it so I have energy and very little pain! I can keep my house clean again and keep up with my two younger children one 13, and the other 10. I don't have to stay in bed any longer during the day and I can be a better parent and spouse to help my husband. I am afraid without Kratom and the vitamins I take, I will go back to the excruciating pain I was in before that opiates don't take care of because you start needing more for them to work! I want to keep being a good Mom and also get a job again and Kratom gave me that hope again! Please don't take this hope away from me and the countless others that take it! I know they are saying negative things about Kratom but I know I have found none of those things to be true. The benefits far outweigh the risks. My blood pressure is now under control and I can live again for years I felt like a useless lump of pain laying in a bed waiting to die and I no longer feel that way. - [redacted] [redacted] [redacted], CA

I am a 43 year old woman who was a teller during a bank robbery in 1999. Since that incident, I have suffered extreme anxiety, including panic attacks, and have had too many occasions of being unable to leave my home due to pure terror at the thought of coming into contact with others. I had received prescriptions for Xanax and Seroquel, but hated the numbness and missing days both caused in me. After being introduced to Kratom in tea form (by a very intuitive friend) approximately five (5) years ago, these attacks and bad days are down to maybe two or three a year, rather than being a weekly occurrence. As an additional 'bonus' during this same time period, I have noticed a huge reduction in the pain from menstrual cramps and associated migraines. I fear that if this plant is banned, I will revert to my previous state of pain and fear, and I would like to avoid this at all costs.
[redacted] [redacted] [redacted] [redacted] [redacted], FL

I am a 57 year old woman with no kids, who is the sole caretaker of my 87 yr old widowed mom. I was diagnosed at 13 w/double curve scoliosis but since we were Jehovahs Witnesses, bloodless surgery was out of the question. The pain, as I age, takes my breath away. I'm on disability because the damage being done to my nerves from the decompressing vertebrae is amazing! Doctors prescribed vicodin and oxycodone for pain. 13 years of taking it and then they couldn't give me oxycodone anymore so the started making me take oxymorphone. It was the only thing that they would prescribe because I'd gotten used to such a huge opiate load. Last Feb 2016, I'd had enough of driving an hour each way to the pain clinic to pee in a jar. Enough of the stigma and feeling like a criminal for being on pain meds. I had read about the herb KRATOM and decided to try it. I'm not going to sugarcoat it. Cold turkey was like living in a Hyronomous Bosch painting but I did it with the help of Kratom! I've been off ALL pain meds since,and using Kratom when the pain takes my breath away. I have my life back. I am of use to society and can care for my mom and home, where before I'd just lie in bed all day,and count pills, wondering how I was going to make them last because there were never enough. Pain varies day to day. What works one day might not be enough the next. Or too much! I knew I had to stop. KRATOM gave me my life back. PLEASE DON'T LET THIS HERB BE BANNED!! It would be a mistake unless the aim is to have the pharms get all opiate users addicted to another drug. I only have to use Kratom a few times a week. Please! Just this once? Let it NOT be about the money for the Pharms? Please?

Hello, my name is [redacted] [redacted]. I am a mother to a blended family with eight children, a grandma to four little ones, a wife, and a full time college student. I also have lupus and degenerative joint and disc disease. I was under a doctor's care for several years, but seemed to just get sicker and sicker. I was to the point I could barely walk, I certainly could not run and play with my children. I was merely dragging myself through the days, trying to make it for my kids--not living, just surviving. As my pain level rose, so did my tolerance for the medications I was prescribed. First it was oxycodone and xanax, then dilaudid and klonopin. But I was not getting any better. If anything I was getting worse. Then I realized I was dependent on the medications, and decided to self-withdraw, with only my husband's and children's support. My husband even tried to convince me that it would be okay to use a suboxone program, and was even willing to take me out of state if necessary, but I refused. I had trusted the medical system and it had failed me. I knew I had to do this on my own. After 14 days of hell that I would wish on no one, I was free of the dependence on the medications, but back to square one with my pain, fatigue, and overall malaise. I began researching for natural alternatives to improve my health and quality of life. That is how I came upon kratom. I decided I had nothing to lose, it was worth a shot. From my first cup of tea made from this precious plant, my life began to improve. I found I could move again, and not that fake energy you get from pharmaceutical painkillers. I slowly started to get stronger, healthier. I could play with my kids again. I could work in the yard. My husband still tried to baby me a bit, but as I got stronger physically, I got stronger mentally and emotionally, and soon he had his tough little woman back. Everything has changed. I have a better life overall. I tossed out the microwave, cook all our food from scratch, try to avoid processed foods (as much as we can afford!), I stopped taking all over the counter medicines, and now only consume safe herbal remedies and alternative medicines that come from nature! God truly has provided us with all that we need; we just have to be willing to take the time and patience to find it! My only bad habit really remaining is that I still smoke, but I went from three packs of mainstream raunchy tobacco to less than a pack of organic tobacco cigarettes a day, and I hope to give those up one day as well. I have had four grandchildren born in this time period since I discovered the benefits of kratom. My oldest two grandchildren are almost two years old (yes, both, one from each oldest grown child!), and they both think Grandma can do anything! I never tire of chasing them through the house, taking them out to swing, or having them help me in the garden. If we go out as a family, I am the one who carries them piggy-back for hours--they are my best little friends! My youngest children are six year old twin boys, and it is the same with them. We were out last weekend playing freeze tag, jumping over their toys in the yard, shrieking and running for base like nobody's business. Please, please, I do not often beg, if ever. But I am damned well begging now. Please do not take this away from me, or from them. I cannot bear the thought of my little ones or my grandbabies reaching for me and me having to tell them Grandma or Moma cannot pick them up. That is absolutely more than I can bear. I do not want to ever let them down. My older children are beginning to forget those dark years of sickness and doctors' offices and Moma laying in bed, exhausted, or crying; it has already begun to fade, and they believe they can count on me for everything once more. My little boys have no memory of that sad, sick broken woman, and my grandbabies never had to meet her, ever! Please, don't re-introduce her now. Thank you.

I am 45 years old and a 27 year veteran of the military. I suffer from chronic back pain (Vertebrae Degeneration). I also suffer from PTSD. I was on an Opioid painkiller for the chronic pain. About 8 months ago I was searching for a natural alternative to RX pain medicine. I found Kratom and it has worked wonders for me. I have not taken a pain pill since. Before the kratom it was hard to function due to the intense pain, now I can do almost anything with very little pain. After taking the Kratom for a while I noticed the effects of my PTSD were noticeably less. I do not have the anxiety like I use to and my sleep is so much better. I pray they do not ban Kratom. I do NOT want to go back to the chronic pain I suffered and I do not want to go back onto pain medication. I am leading an active life and my quality of life is much better with the Kratom. I have also introduced Kratom to many veteran friends of mine and it has also helped them tremendously! So please keep Kratom legal for those of us who need it.

My name is [redacted] [redacted], I'm 36 years old, a father of two and one on the way. I am the sole provider for my family.

I was diagnosed with Crohn's disease back in February 2015 after having a large section of my colon surgically removed. In the months leading up to this I was in excruciating pain because my intestines were completely blocked from inflammation caused by what I later learned was crohn's disease.

I still have frequent flare ups that cause me a lot of pain and discomfort. I am prescribed narcotic painkillers to help cope with that. I take them regretfully, when I do take them. I understand the damage they do to the liver with all the acetaminophen. They are highly addictive, I can't focus when I take them and they make you feel miserable.

When I realized that I was actually becoming dependent on prescription painkillers, that's when I started looking for an alternative. I lost a brother to an overdose on prescription pain pills, I've lost several friends as well. We're not talking about your everyday addict either. I'm talking about good hardworking people that had a legit reason for taking the very medications that cost them their lives.

Again, regretfully I still take the pills I'm prescribed when I have a bad flare up. The only reason for that is the cost. I have insurance, so it's a lot cheaper to get a prescription under my insurance that it is to buy Kratom but for someone without insurance, it would be a lot cheaper for them to buy Kratom.

Money aside, my plan was/is to get off the prescription medication all together with Kratom. In the meantime, it has allowed me to take the pain pills a lot less frequently and I have been able to transition from pain pills to Kratom without any side effects. I'm not an addict, never have been, I have to give Kratom a lot of credit there. Without having this amazing plant to fall back on.... who knows. I like to think I'm stronger than that but so was my brother.

Aside from the pain, Kratom has also helped with slowing down spasms in my intestines. When I have these spasms, you can see my abdomen contracting, Kratom seems to slow that down within 20 or 30 minutes after a glass of Kratom tea. It also help with regularity, I hate to go here, but it's an important issue and I think this could really help a lot of people.

My father has also benefited tremendously from Kratom. He is 76 years old and has been on pain pills for about 9 years! Well.... not anymore. He has not had a pain pill in over a month and his withdrawal symptoms have been almost non existent. Before we found Kratom, you couldn't even get him out of bed if he didn't have his pain pills. The symptoms were so bad for him, I couldn't bear watching him go through it! Vomiting, diarrhea, sweats, nausea and then there's the depression! Wow, it was bad. Not anymore. He actually asked me to pick him up and bring him to buy a car!! He hasn't been out of the house in months, let alone had a desire to drive anywhere or do anything.
I have a few other testimonials that I could share with you but for one, they're not mine to tell and two, I am a responsible adult with a family to provide for and a job to go to early in the morning and yet, here I am sitting here at midnight writing this letter to plead with you to help us fight for this amazing tea leaf that provides miraculous relief & benefits for myself and countless others.

My name is [redacted] and I am 34 years old. I am a successful business owner and a regular, tax-paying citizen with a great family. Through no fault of my own, I suffered a bad accident and live with the pain every day. I took narcotics for years and had to stop because I realized that they were doing much more harm than good. My family said that I was a different person, and I was. I found Kratom a year ago and it was like a curtain was lifted. It is not a cure for anything, but it’s indispensable for me. It simply makes life more manageable for me with less side effects than narcotics. What people who have never had chronic pain before don't understand, is that taking nothing is not an option. If this ban goes through I will have to choose between going back to dangerous pills, living my life in pain again, or keep taking kratom and be labeled a criminal. Just when I finally feel like my life is under control and I am happy again, the very people who are supposed to protect my rights are stripping them from me. I honestly don't feel free anymore. All this ban will do is cause people who have suffered all their lives to suffer even more. People will die because of this, and it is inhumane and immoral. What we need is more information and regulation. Please do not take this choice away from us.

My name is [redacted] [redacted]. I am a 37 year old and I suffer from sacroiliac dysfunction, degenerative disc disease and have two torn annular fibers in my lower back. The doctors currently can do nothing to heal me and have told me directly that the best they can do for me is keep me “comfortable” by prescribing medication. The surgery that they could do is only 40% effective and could potentially lead to more pain not less. I’ve had this pain for 4 years now and it’s sad to know that it is something I will deal with all my life. Kratom allows me to avoid being a haze all the time due to the Vicodin/tramadol/Lortab and other meds I was prescribed. I can function again. I find that kratom is more effective than any of those pills. If the ban goes through I will be forced to return again to the pain doctors and to have painful injections in my spine. I don't believe they help but they appease the pain doctor so that he feels he is at least trying to take steps outside of just prescribing meds. Truth is they hurt like hell and don't work and sometimes actually do more harm than good as they make me aggressive and I am in pain for weeks after getting them. I will have a life of addiction and pain doctors in my future if this ban goes through.

My name is [redacted]. I am 31 years old and have been using kratom daily for the past few years. I have struggled with depression and anxiety for most of my life, and am recovering from past traumatic experiences. I take prescription medication for my symptoms. Though the medication does help somewhat, I remain symptomatic, and kratom is the only thing that has made me feel truly happy and optimistic. It has helped me to become more productive and socially engaged. I was miserable for years prior to incorporating kratom into my lifestyle, and since I began preparing this herbal tea on a daily basis, I have felt happier and more fulfilled than I have in a long time. The great thing about kratom is that it makes you feel good enough to make you want to do OTHER things that make you feel good, like live a full life without fear, worry, self-doubt, misery, or regret. By becoming more socially engaged and productive, depressive symptoms become even less likely. Without kratom, I will be in very real danger of resuming past self-anaesthetizing behavior, including excessive drinking. Obviously, alcohol consumption is NOT conducive to productivity, and problem drinking is not conducive to positive social engagement. I do not wish to return to those dark days, but in the absence of a reliable substitute to treat my symptoms, I fear I will have no choice. I fear I will become chemically dependent again, my life will fall apart, and my health will fail, just as it happened before. I am a college-educated professional trying to start my own business, and I have served my country in the Peace Corps. I am generally a good, kind, responsible person, who is simply in pain. I had limited options for properly dealing with this pain, especially during times when I could not afford health insurance. Even when I can, prescription meds can only do so much. Discovering kratom was nothing short of miraculous to me. After so much trial and error, I found a sustainable way to manage my symptoms, and just as I get my life together, that miracle is being taken away as a result of misinformation. Kratom is not a dangerous drug. It is an incredibly helpful herb with enormous potential to help people with chronic pain, whether physical or mental, live a happier, healthier, better life. Please don't take this miracle away from me and turn me into a criminal with this ban. Kratom gave me my life back, as it has for so many others. For that, it is something to be celebrated, not banned.

My Name is [redacted] [redacted], I am 36 years old, a father of two and one on the way. I've been taking Kratom for over 6 months now. It helps tremendously in relieving the pain associated with crohn's disease. As the pattern goes, I'm prescribed percocet to help manage that pain but I've found that Kratom is a much better alternative.

My name is [redacted] [redacted]. I am a veteran of foreign wars, have been employed in the engineering field for 37 years, and now retired at age 65. My aging process has brought on chronic arteritis - causing me to have to rely on aspirin and other NSAID pain medications related to causing heart problems and or gastric problems if taken for too long. While looking for alternative pain medication, I ran across Kratom. Kratom has given me the ability to function most of the day, basically pain free while taking care of the day's work/tasks. Taking the right amount of Kratom to relieve the pain has an effect of taking approximately (2) cups of coffee, and that's it! Would hate to have to revert to the more dangerous pain medications!

[redacted] TESTIMONY - I am the face of a chronic pain sufferer. In 2001 I was diagnosed with Fibromyalgia and immediately placed on the pharmaceutical superhighway. With each new side effect of a previously prescribed drug, I was given yet another drug to take. After being on the strongest pain med available (fentanyl patch) along with antidepressants, muscle relaxants, and various other meds I had finally had enough. No person should have to live their life around the schedule of taking 15 different medications! So I decided to go a more holistic route and discovered a miracle herb called Kratom. With this wonderful plant I was able to wean off many of the prescriptions, therefore reducing the many side effects of those drugs. In addition, my quality of life improved tremendously. I was able to get out of bed, take a shower, go to the grocery store, cook dinner and visit with family and friends. I also no longer had to depend on alcohol to self medicate what pain the pharmaceutical drugs didn't touch. Using this God given natural medication allowed me to focus again on something other than my pain. It gave me energy where before I had none. And I began to live life again. Now the government intends to ban Kratom turning all those benefiting from its healing powers into criminals overnight! Well I say no more! Where are my unalienable rights that are guaranteed in the Declaration of Independence upon which the government is supposed to protect? Why don't I have the right to pursue happiness? Where is my liberty, my FREEDOM TO CHOOSE? It should be illegal to criminalize nature! We Americans should not be mere pawns in the DEA and big pharmas game of chess. Many chronic pain sufferers will have no choice but to be bedridden again. Many will go back to being drug addicts as well. Not by choice, but by necessity. If Kratom does indeed become illegal, some of us will not even survive. I know of many military vets whose lives have been saved due to Kratom. Those who fought for our freedom, why is our government now taking away theirs? And mine. I don't want to go back to that place, that place of being a non-functioning, unproductive, bedridden sick person, instead of the vibrant person I've become thanks to Kratom. It is not a road I want to go down again. When the greed of our government overrules quality of life there is no justice and all is lost. When you can't live life free from pain by using what nature provides, so others can line their own pockets, there is no freedom, only pain.

My name is [redacted], and I'd like to share a little bit about the role kratom plays in my life. I am a 44 year old educator for a world renowned science institution, an artist, and a father and husband. I consider myself to be an upstanding citizen and a positive contributor to our society. For the past 25 years I have struggled with a variety of mental illnesses including Major depression, Generalized anxiety disorder, Panic disorder without agoraphobia, and alcohol abuse disorder. The symptoms of these conditions are sometimes debilitating. Even on a good day I am operating at 40% of my potential capacity. Through some miracle, I have managed my life despite these challenges but, once again, not to the best of my ability. I discovered kratom 2 years ago, and the transformation has been almost unbelievable. I have tried so many different medications. Antidepressants, anxiolytics, mood stabilizers and antiepileptics. I have taken part in CBT, MBCBT, DBT, group therapies, and twelve step programs. All of these traditional therapies have been effective in one way or another but none alone, or in combination has provided complete relief, and the medications come with assorted side effects that are, sometimes, worse than the conditions they are meant to treat. I turned to alcohol for temporary relief and quickly descended into active alcoholism. After hospitalization and rehab, I have managed to achieve and maintain sobriety for 7 years but that comes with challenges of its own. Kratom, a simple leaf from southeast asia, has completely changed the quality of my life. Not only has it caused almost complete abatement of my symptoms (I'd put my function at 90% as of this moment, it is after all not a complete panacea) but promoted wellness in other areas of my life too numerous to detail here. I am a better father and a better husband, a better teacher, a better contributor to society as a result of this leaf and, finally, I have found contentment that I once thought impossible. All of these changes have come with nearly zero unwanted side effects. I consider this a gift from god, this leaf. Created as a benevolent aid to a life of wellness. It is no mystery to me that Buddhists consider this plant sacred and use it as an aid themselves. To take this gift from we Americans who through its assistance have found broken lives and bodies made whole again would be, in my opinion, an act of violence against god and nature. A destructive act that would cause irreparable harm to those who use this botanical. The results would be a return to sickness, addiction, and detrimental effects on the economy through loss of jobs and income and the added strain on the American health care system. People will die as a result of the DEA's rash and unconstitutional actions.

This my perspective and this is my story. I thank you for listening and beg you to consider these words and those of the others who join me in sharing them. May god have mercy on our souls.

Hello, my name is [redacted]. I'm 49 years old, and have been drinking Kratom for 6 years. I spent all of my career with the exception of the last 5 years, working as an automotive painter. I'm currently an internationally published commercial photographer, having had my images published in The Grammy's Program, NBA Finals Program, Major League Baseball All-Star Game Program, and Paula Deen Magazine, just to name a few. Having crawled around on my knees on concrete floors in body shops for the better part of 30 years, and the last 5 years, spending long days on my feet and carrying heavy gear all day, I now suffer from chronic knee and lower back pain. The pain is so intense that standing up in the middle of the night to walk the bathroom is excruciating. My doctor has tried prescribing different mild pain relievers (I won't take the heavy narcotics, because I refuse to get addicted to them), and nothing has even remotely helped. Then I was introduced to Kratom Tea by a friend who was in a similar situation due to intense pain. Since that evening, my life has been changed. Now I can exercise again, run with my dogs at the park, ride my bicycle, bowl, and an entire host of other things that I thought I would never be able to enjoy again!! I'm even going out with my camera to shoot landscapes and bands, just for fun. I'm so excited because photography has been my passion since the 8th grade, but the intense pain, turned into a miserable day at work! Kratom Tea has saved my life, and made it a life worth "living" again!!!

Hundreds of thousands of people are experiencing this every day due to this amazing plant, with no side effects. Please don't take that away from us. There's nothing wrong with Kratom, and there's no reason Kratom cannot exist alongside the poisons provided by pharmaceutical companies. A lot of good people will suffer, and those fighting addiction using Kratom may even die, and for what? So big companies get richer than they already are? When do "We the People" start to matter again?!! How much money is enough? It's time for someone to step up and tell the pharmaceutical companies that they refuse to be bought out, and what they want isn't good for the people of our great nation. Everyone on these pages are begging you to "Please stop this ridiculous ban on Kratom!!" Our quality of life is in your hands, don't let us down!!!!
[redacted] in Florida

Hello, my name is [redacted]. I'm 49 years old and have been taking Kratom for 2 years. I broke my back when I was 19 years old. Two back surgeries. I managed without anything for about 10 years and then felt I needed something to deal with the pain. I went back to orthopedic and they suggested another surgery. I couldn't deal with another surgery. They sent me to their pain management doctor. I really didn't know what I was getting into but trusted the doctor had my best interest. Was prescribed hydrocodone. I said wow, I think I can deal with the pain now. Well like a lot of people, all the doctor gave me was an addiction that would define the next 15 years of my life. In the end I turned into an animal an eventually turned to heroin. Then went to treatment inpatient. Detoxed but still couldn't deal with the pain and turned back to pain pills. I then found suboxone, thought this was the answer. Just another trap. Finally found Kratom! I was able to get off the suboxone and I take a total of 2 teaspoons a day of Kratom. My life is totally transformed. Now you're trying to take that away from me. I really don't know what I'm going to do if this happens. I can't go back to that other life, I will die for sure. Anything that can keep Kratom available I am all in!! I was able to save a marriage of 28 years, I have two grown children and hope to see my grandchildren grow up. Kratom works!!

Hello my name is [redacted] and after a serious car accident I was prescribed Vicodin. It didn't take long to go from 2 a day to 2 an hour. Once my doctor stopped prescribing them to me, I was hooked and needed to continue my habit. I switched to buying them illegally for two years. I lost everything because the pills were my only focus. Not family, not work, not anything. When I finally decided to kick the habit, I was told about kratom. I believe without Kratom, I would be dead right now. It not only manages the constant pain I still have because of my accident, but I am no longer a slave to the pills.

My name is [redacted]. I am 39 years old. I am a mother of two. I teach martial arts and am currently in a program to receive my certification in personal training. I love playing sports and am extremely athletic. In the past two years I have had to have three surgeries from injuries I have sustained from my extremely active lifestyle. As a result of my many injuries, I have arthritis and bones spurs in my knees. I wake up every morning barely able to walk. I drink my kratom tea in the morning and I am able to walk pain free and am able to live the quality of life we all deserve. I have no desire to be prescribed pain medication.

My name is [redacted] and this is how kratom has changed my life. In 2008 at the age of 30 I was told I had a giant Tarlov cyst. I had a spinal surgery to try to drain my cyst that was on my spine in my sacral area, this did not work and I developed a spinal fluid leak. Again I went for surgery to stop the leaking, again no luck. I then was transferred to a third surgery three hours away. This did fix my leaking but unfortunately I had leaked too long and ended up with another very painful condition called Adhesive Arachnoiditis. This condition causes me pain to the point where I can't sit on my tailbone very long at all, which left me in bed almost 24/7. I was prescribed fentanyl and was miserable on it for 7 yrs. I was foggy and not aware of what I was doing while on that medicine. I met a special lady who told me about Kratom and what good it was doing for her. I started slow and read a lot. I found myself, that it was changing so many lives of my friends. I too became brave enough to attempt to come off the fentanyl. Today one year later I'm off fentanyl and out of bed. I'm clear minded and actually have times that I'm out of bed by 50% out of my day. I'm more stable than I have been in eight years. PLEASE Don't make kratom a schedule 1 herb. I would like to keep getting the most out of life naturally. Thanks for reading [redacted] [redacted]. [redacted]

My name is [redacted]. I'm 31 years old. I've been a regular consumer of Kratom for about a year and a half now. My main reason for using the plant is to combat consistent depression that has been affecting me for much of my adult life. I also have been addicted to opiates in the past (from about 2006-2015 off an on) and Kratom helped me get off of them and live a normal life. I do not have cravings for opiates, and it provides me with a little bit of energy, mood-lift, and motivation--much in the same way coffee does, without the edge. I make tea out of the powdered leaves. I do not get "high" off of Kratom. I am an average working class American who uses an herbal supplement because it helps me with very few side effects. Antidepressants have not helped me. If this is taken away from me, I am extremely worried about my mental health, in addition to the possibility I might relapse back into opiate addiction. I am extremely upset that I have to justify my usage of tea to my government, especially when the reasoning was factually skewed and done without public comment or research. It feels like a violation of my god-given right to help myself live a normal productive life, with a plant that has shown to be extremely effective and safe.
[redacted] [redacted] [redacted], NC

I am a 32-year-old female who works as an Assistant Professor at a state university. About a year ago, I was crossing the street as a pedestrian and was struck by a car travelling approximately 25 miles per hour. The accident resulted in serious soft tissue damage to my knees and back, including several herniated discs in my cervical, thoracic, and lumbar spine. The cervical disc herniations caused compression of my spinal nerves in the neck area. These injuries resulted in weakness, numbness, and sometimes debilitating bouts of pain. My back pain has been so significant as to force me to spend huge portions of my life on the couch and to prevent me from eating normally due to the excruciating pain associated with even minor movements such as opening and closing the jaw. Without forming an addiction, I have used kratom as an effective pain treatment for these symptoms, one that is less harmful, in a number of dimensions, than the prescription pain medication I have also been intermittently prescribed. I am concerned that this step by the DEA would either lead to more individuals with reduced quality of life due to chronic and significant pain or to reduced quality of life due to addiction to prescription pain medication. In the latter case, people also risk side effects, including death, associated with prescription pain medication as well as the social and medical consequences associated with maintaining an addiction.

My name is [redacted]. I am a 58 year old male. Kratom stopped me from drinking. I got much healthier with kratom. Now I have to go back to alcohol which is much worse. The DEA’s decision will cause the deaths of thousands and will cause great human suffering.

My name is [redacted] [redacted] . I am a married father of three school age children. I am former NYC firefighter. I am a collapse survivor of both towers on 9/11/01. I suffer from PTSD due to my experiences and efforts on 9/11 and during the rescue and recovery in the aftermath. I have been prescribed anti anxiety and anti depression medications which I do not feel are helpful. I also DO NOT like to take prescription meds of this or ANY type. I Do NOT take illegal substances or drugs. I DO NOT drink alcohol. I DO NOT seek any type of “high or euphoria”. That is NOT what Kratom is. That is NOT what Kratom does. I use Kratom as a tea or with orange juice. I find it helps relieve PTSD symptoms. It does not erase these extreme symptoms but helps to make them more manageable and less debilitating and this helps me to lead a life that is more manageable and fulfilling. The proposed Kratom ban is an unfair rush to judgement based on a total mischaracterization and misunderstanding of this natural herbal supplement that is being used to help so many people. A Ban like this will surely make my life much more difficult and my daily struggle to manage symptoms much more debilitating. My life will certainly become infinitely more difficult. Why would the DEA or the Government rush to judgement on this based on what can only be described as a lack of information and research. This is an unjustifiable overreach and an unfair rush to judgment that will surely impact many good people in a very drastic and negative way. Good people are trying very hard to manage their illnesses and conditions and this Kratom Ban will surely increase their suffering. Isn't that exactly the opposite of what the mission should be? Please take a closer look at this before letting this ban go into effect.

My name is [redacted] [redacted], I am a 30 year old mother of 2. I suffer from chronic back pain due to DDD and sciatica, anxiety and depression. I began consuming kratom on day 7 of opiate withdrawal from Dr prescribed opiates. When they stopped working and I asked for something different I was immediately cut off and fired as a patient. He has since quit practicing. I found kratom and it helped me get through the worse of the withdrawals. I continue to use it for my many diagnoses. I have found a quality of life I never knew existed. I am not high. I am not impaired. I am terrified of going back to opiates, anti anxiety meds and antidepressants. I will likely be bed ridden most days with a feeling of dread for each day. My anxiety was debilitating even on benzos .What will become of my children mother? What will become of me?

My name is [redacted] and I have used kratom for anxiety, depression, and fibromyalgia. It has eased my issues in a natural way without the need of prescription drugs which cause even worse issues in themselves! We deserve a natural option to treat our health issues. Please help keep kratom legal and help the states where it's been banned make it legal again !

My name is [redacted], I am a mother, wife and a systems engineer. I have worked since college (a Bachelors in Computer Science) and have never been a burden on anyone. I don’t smoke or drink, nor have i ever done illicit drugs and never looked for a high or any kind of euphoria. I suffer from painful injuries sustained from my days riding horses and competing in jumping events. I also fell down some hardwood stairs when i was pregnant, and to save my baby, i took the brunt of the impact in my back. I have also suffered PTSD and depression from a childhood trauma. I have taken regular pharmaceuticals prescribed to me without much effect, and with terrible side-effects. I discovered Kratom 3 years ago via a herbalist and I have never looked back since. This plant has given me back my quality of life that every person has a right to live. This proposed ban is cutting a lifeline for so many people, this does not suggest an agency working for the benefit of the people, but very much against them.

My name is [redacted]. I'm an award-winning author and a grandmother. I am also bipolar, so using common pharmaceuticals is not an option for me. Any prescription med that warns of mood changes or suicidal thoughts is like kryptonite and dangerous for me, so I must use alternative medicines for most things. I deal with chronic pain from fibromyalgia and a back injury, and opiates are not an option, either. Kratom has been a godsend! Not only does it help with the chronic pain, it helps me sleep and helps me moderate my moods. Placing Kratom on the Schedule 1 list will diminish the quality of my life by an order of magnitude. Please, reconsider and don't make me into a criminal for using a substance that God made.

My name is [redacted] [redacted], I am a 36 year old male from Kansas. 10 years ago I had a major knee operation which did not go well and never healed properly. During this span of knee surgeries, doctors gave me thousands of painkillers without a 2nd thought. I became addicted, to the point where i was buying them on the street once i was cut off. The day i found Kratom was a beautiful day and allowed me to turn my life around. On top of that, my sister was an even worse case and Kratom truly saved her life. Do not let them stomp on our liberties, this plant should be revered, not banned. It saves lives and allowed my family to go back to normalcy.

My name is [redacted] and I suffer from chronic Lyme disease. Before kratom I was in pain all the time. Kratom gave me the ability to start living my life again. Prescription pain medicine didn't even help the pain. If kratom is banned I don't know how I will make it sometimes the pain is unbearable. I don't want to feel like that again.

My name is [redacted]. Herniated & ruptured discs, degenerative disc disease, unsuccessful surgeries, Fibromyalgia, anxieties and depression brought on by these illnesses, opiates and other prescription drugs, and the guilt and failure I feel as a mother have all robbed me of any quality of life for the past 20 yrs. Earlier this year I was blessed to have found Kratom. With Kratom I have been able to stop all medications. I am able to live free of my round the clock pain, able to know what sleep is like again, able to function a more normal life on a daily basis, every single day! Most importantly I am free of the guilty feelings of failing my children. Kratom has given me a true quality of life back. I now fear I will have to live the rest of my life as I have for those 20 yrs past, I deserve to live free of that pain but without Kratom it just doesn't seem possible.

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name is [redacted] [redacted]. I'm a 51 year old former RN. Former due in large part to fibromyalgia, which was diagnosed in 1996, becoming increasingly worse over the last 20 years. I also have osteoarthritis (diagnosed 1996 as well), sciatica, anxiety and depression. Over the last 20 years I have been prescribed a multitude of medications. Some worked ok-briefly, some a little, some not at all. They all had a boatload of bad side effects. I began managing my symptoms with kratom about two years ago after an RN friend of mine recommended it to me. Much to my surprise it provided more relief than any of the pharmaceuticals I have tried, with minimal side effects. Really the ONLY side effect I have is constipation, which is easily managed. I experience NO high or foggy feeling. I can manage my symptoms with kratom well enough to allow me to care for my aging parents. Without kratom (which my mother also takes for severe arthritis) I am scared to death of how I will be able to care for them. Yes, I probably could get a Norco prescription again, however I would rather not. To avoid dependence on Norco I only took it a few times a week at most, waiting until my pain was severe enough to be in tears. I do not want to return to that existence. That is no way to live.

My name is [redacted]. I am a 38 year old wife, mother and small business owner. I suffer from chronic headaches including Episodic Paroxysmal Hemicrania, back pain from herniated discs, an annular tear and pinched nerves, and debilitating abdominal pain from IBS. I have been to countless doctors who have prescribed about 50 different medications, and none of them have really helped but several of them have caused terrible side effects. I would sit in the office of a pain clinic for 3 hours only to be prescribed narcotic painkillers that left me feeling high and nauseous, and seriously clouded my thinking. I discovered kratom about a year ago when someone suggested it as a natural alternative to prescription drugs. I did some research first and was unable to find anything that indicated that it was dangerous, so I tried it. I was skeptical but when I tried it I was amazed - it made the pain tolerable without making me feel high, and if I didn't take it I didn't experience any withdrawal symptoms. I was especially pleased with how it worked for my IBS. The cramping stopped, and I became "regular" again and was finally able to eat normally. I also became much happier because I was able to run my business and spend time with my family without being in constant pain or just feeling too sick to function. If this ban goes through I don't know what I'll do. Kratom has allowed me to stop all 5 of the drugs I was taking daily (some to treat the side effects of others), and now I can't bear the thought of going back to prescription pain meds.

My name is [redacted] [redacted]. I am a 46 year old industrial maintenance technician for over 26 years. I have suffered from degenerative joint disease for over 8 years in my hips, knees and lower back. I was prescribed percocets and fentanyl patches for my pain for 6 years. I became severely addicted to synthetic opiates because of this. I hated the fact that I had to depend on these opiates just to function and work everyday. I found kratom 9 months ago, after doing research for natural pain relief. I cannot thank the discovery of this plant enough for giving me my life back, free of opiates and being able to have a clear mind. This plant has honestly saved my life. A plant that can relieve pain like kratom does and breaks the cycle of opiates abuse when I thought I would never be able to get off them, should be kept available to us. This plant has honestly gave me my life back, even though I still have the DJD, I can function, with a clear mind and enjoy life again.

My name is [redacted] [redacted]. I am 36 years old, a mother, & a wife, & a small business owner. I also have endometriosis, herniated disks in my back, & hip dysplasia. My whole life all I ever wanted was to be a mother. Only 2 years ago I was practically bed ridden & was told by several doctors I should start preparing for back surgery. I had to take my new baby to doctor's office after doctor's office and he watched as I was prescribed pill after pill. 11 medications in total including several narcotics specifically 100 percocets a month.This was no life. And I was not the mother I wanted to be. I was in pain but in so much of a fog that I just wanted to sleep. I was riddled with guilt every single time I opened a pill bottle and my son had to watch while mommy took her medicine. I was hopeless, depressed, and fighting anxiety because I felt so stuck. Don't worry they gave me a pill for that too. I stumbled upon kratom after trying to find an alternative to the harmful medications I was taking. I was interested because it is 100% natural & had been around for centuries with no reported deaths or overdoses and no real side effects. Especially in comparison to the chemical cocktail I got filled at the pharmacy every month. I felt like I found a miracle. And it truly is a miracle that this plant just grows on the earth and can & has helped so many people. Now my life is mine again. Mine and my son's and my family's. I was able to begin taking yoga classes and started seeing a chiropractor. No surgery. No pills. I haven't taken so much as a Tylenol in over a year. I can play with my little boy and make plans for the future because we are all healthy now. When I think that I might have to go back to that life on the couch riddled with pills and hopelessness it is too much to bare.

Please do not make kratom a schedule 1 drug. Please just learn the truth about what it is and what it is not. It is not an opiate. It is not a dangerous chemical. It is a plant. A natural miracle. And we kratom users are not addicts. We are mothers and fathers. Husbands and wives. We are teachers and nurses and small business owners who don't wish to be heavily medicated by the prescription drugs that are poisoning our country. Please make your decision based on facts and science not media hype and misinformation. Thank you very much for your time. Sincerely, [redacted] [redacted]

My name is [redacted] [redacted] [redacted]. I discovered Kratom 3 years ago when my back pain got really out of hand. I was literally spending most of my days in bed because the pain got so bad I couldn't function. I have 3 children so I had to look for a way to control the pain without the side effects from opiates that would leave me sleeping more than being awake. I discovered kratom. I did a lot of research before ever taking a pill. I wanted to make sure it was safe for me. So after my research I was comfortable enough to order some and try it. It starting working on the pain for day 1. It gave me energy and made me feel so much better. 3 years later I am now back to working and raising my children like I was before my back took me down. I have scoliosis and sciatica. The pain would get so pain I couldn't even stand and now I work as a housekeeper at a hotel. Kratom gave me my life back. Opiates always left me in a haze and I couldn't raise my children feeling high all the time. I also feared taking opiates because I didn't want to get addicted so I am so thankful for Kratom and I know many many more feel the same way. Stop trying to ban a coffee plant and focus on the prescription drugs that are the real problem. Please stop the ban!
Sincerely
[redacted] [redacted] [redacted]

My name is [redacted]. I was diagnosed with fibromyalgia and chronic fatigue around 15 years ago. I also have some neurological problems, including chronic migraines and restless leg syndrome and have spent more than my fair share of sleepless nights. I also had pneumonia several years ago that left me with scar tissue in one of my lungs. It burns every now and then and is quite painful at times. All of this has severely impacted my ability to work full time, which I haven't done in 12 years.

I've been put on many pharmaceutical medications over the years, including Neurontin, Cymbalta and Vicodin, which all helped ease my pain, but turned me into unemotional zombie. I cannot take NSAIDS due to another medical condition and I don't take pain killers unless I'm really hurting. But since taking kratom I haven't had to. I also suffer from depression and anxiety and the Cymbalta, which helped the fibro pain, really wasn't addressing the depression/anxiety issues, even though it's supposed to. So I started looking at alternative options, including botanicals.

I learned about kratom nearly seven years ago and decided to give it a try. It has been a godsend for me. Not many people were talking about it when I first started taking it, but all I knew was that it helped me not only to be free of pain, but it also gave me enough energy to be productive and get through my day. I found that after 10 years of sleepless nights, I could get a decent night's sleep.

I don't consider myself a drug addict. I'm a 61 year old woman who suffers from pain. Kratom doesn't get a person high and you can't overdose on it (you will get sick if you take too much). I do not want to become a slave to opiates. I'd rather be in pain, but I honestly don't know what's going to happen to me and so many others if this ban takes place.

Hi, I'm [redacted]. A senior citizen, wife, mother, and grandma. I have suffered a non-cancerous brain tumor, which left me deaf in one ear 17 years ago and caused other cranial nerve issues to set in. I have Hashimoto's autoimmune thyroiditis, trigeminal neuralgia (one of the so-called "suicide diseases" due to the extreme pain it causes), herniated discs in neck, daily migraine for 32 years, spinal stenosis, generalized anxiety disorder, and end-stage neurological Lyme disease diagnosed last year but likely acquired at least 25 years ago. I have been on many medications for the above conditions, all legally prescribed and taken as the doctors ordered. I use no alcohol or illegal drugs and seek no highs from medication---only relief from symptoms. A year ago, I learned about Kratom and tried it, since RXs provide me such limited help. I have found Kratom to be wonderfully beneficial in remediating many of the terrible effects of the conditions I am faced with. It helps lessen my pain and makes my days and tasks far easier to manage. My life without Kratom will be difficult to bear. Please reconsider any proposed ban. Thank you.

My Name is [redacted] [redacted]. I am a 10 year veteran of the United States Navy and I have used Kratom occasionally over the past 4 years to manage symptoms of anxiety and depression. I chose to take kratom as a natural and more therapeutic option and have had great success in using it. I did not like the prescription anti-depressants given to me because I had adverse reactions to 3 different ones I've been prescribed and it was effecting my daily life. With Kratom I have been able to function as a normal member of society. I feel like kratom is just therapeutic enough to take the edge of. I cannot fathom the reasoning behind an all out ban on this tea leaf and implore you to reconsider and think of the thousands of people this will adversely affect. I live my live with integrity and I am certainly not a criminal. Thank you.

My name is [redacted] and I am a 36 year old computer programmer working for a startup in California. I am also a veteran of the US army infantry, having served twelve years and multiple combat tours. I have been diagnosed with chronic PTSD and other conditions which cause chronic pain in my back and knees and hands. The VA put me on many different pharmaceutical prescriptions to manage my PTSD symptoms, and opiate painkillers to manage my chronic pain. But as a computer programmer, it became virtually impossible to do my job on all of these medications. They also didn't work very well to fight my symptoms. There was a time in my life after I got out of the military where I couldn't leave the house. My life was in shambles, even with the medication. I started researching alternatives and found Kratom, a plant from Indonesia in the same family as the coffee tree. After talking it over with my VA doc, I decided to try it. Within a couple of hours of trying Kratom for the first time, my back pain was nearly gone. Over the next few weeks, I also discovered that Kratom helped tremendously with the anxiety and depression of PTSD. I was able to return to work, even starting my own business. I would say that nowadays, thanks to Kratom, I am just a regular person. I provide for my family, I am active in their lives again, and I work full time. When I take Kratom, I pay my taxes.

My name is [redacted] and I am a 36 year old Security Engineer from [redacted], WA. In 2012 I was diagnosed with cervical cancer and after 3 surgeries I was left with chronic pain which left me bedridden most days. The doctors provided me with all types of pain killers which still left me bedridden and unable to work due to their side effects. I would be slightly out of pain, but be too "high" to function. In 2013 I was introduced to Kratom by a friend who was utilizing it for her fibromyalgia. I tried it soon after and was amazed at it effectiveness. I was pain free, had some energy and it did not have the "high" that narcotic pain pills have. I have been using Kratom ever since and it has given me my life back. I am now working which I could not do before, I am able to fully function which I also could not do before.

Not long after I tried Kratom I began reading what could only be described as propaganda against Kratom on different media outlets. There were misconceptions that Kratom was the new pain killer stronger than Morphine that cause relapses in opiate abusers. There were reports of deaths, however they were not proven to be caused by Kratom, just anecdotal evidence stating Kratom was the cause. For example there was recently a death attributed to Kratom by a mother who's son had committed suicide and she blamed it on Kratom since she found empty packets in his room. The young man was also on a mired of anti-depressants which are known to cause suicidal thoughts in young people. Correlation is not causation and I have not seen one credible death linked to Kratom where the cause of death was proven to actually be Kratom. I would like to also mention that while 15 deaths have been erroneously linked to Kratom, Four deaths in the UK and up to 60 worldwide have recently been directly attributed to the substance 2,4-dinitrophenol (DNP), an industrial chemical that has become popular among people wanting to lose weight, including bodybuilders and people with eating disorders, however this is not on an emergency list for Scheduling. The DEA notice also attributes over 600 calls to poison control, however to put that in perspective poison control received 4201 calls in regards to energy drinks and caffeine in 2013 alone.

Current peer reviewed studies on Kratom and its constituents have shown that Kratom has no acute toxicity, displays powerful antioxidant and antibacterial properties, assists with drug and alcohol withdrawal symptoms, contains several oxindole alkaloids which have exhibited potent immunomodulatory properties, and even contains constituents that have exhibited anti-cancer properties! A brief search in any scholarly database will present many peer reviewed studies and clinical trials that can attest to the medical potential of this plant. In short, Kratom does not present a significant threat to human health or safety on any level and does not belong in Schedule 1, period.

If Kratom does end up on Schedule 1, even temporarily, we will never be able to research this natural plant as a medicine because as we all know once this has been put on Schedule 1, it's not coming off. Marijuana is a great example. Adding it will make it almost impossible to do the research necessary to show the medicinal benefits. Kratom has been used for hundreds of years in Thailand and is currently banned, but Kratom, also known as Thang, Thom, and Biak, was not originally banned because of substance abuse. When the Thai government started levying taxes from users and shops involved in the opium trade many users switched to Kratom to manage their withdrawal symptoms. The Greater East Asia War in 1942 and declining revenues from the opium trade eventually suppressed the opium market competition by making Kratom illegal. Thailand is now looking to legalize Kratom once again as people have been using this for thousands of years with no cases of overdose, psychosis, murder, violent crime. Never in all of recorded history.

Not to mention this plant is saving lives. People that were addicted to opiates are being helped by it and getting their life back. That is not because Kratom is the same as opiates, because it isn't. It doesn't get you high, it takes away the withdrawal symptoms associated with strong opiate pain killers. Kratom was something they could use to manage their disease on their own time. It was easily accessible and affordable unlike the other options such as Methadone or Suboxone which is hard to get on a program if you don't have insurance or can't afford the drug. Now, with the DEA taking away that option I'm afraid people are going to go back to whatever they were doing before causing the death toll will skyrocket. If you want to save lives and keep people safe as you claim, you will keep Kratom legal.

I do understand there should be some regulations concerning Kratom, such as the "extracts" and "drinks" that people have made and added other known or unknown chemicals. These should be regulated, but I would ask that whole leaf remain obtainable.

In closing I would kindly ask you to please don't take my life away again. I am a mother of 4 who has to work full time to support her family and I am unable to manage my pain effectively in other ways. Me and hundreds of thousands of others are begging you to reconsider this decision and look at both sides of this situation, not just the unproven fear driven side.
Sincerely,
[redacted]

My name is [redacted] [redacted]. I am here to say that as a 64 year old woman I never thought that I would take something like Kratom. After many decades of pain due to spinal stenosis and fibro and trying all that the doctor's told me to try; pain pills, antidepressants, spinal blocks, physical therapy, I finally just didn't use anything for years because none of those things worked and why should I spend money on something that didn't work and could potentially make me an addict or worse. So after going another decade just getting by because of constant pain and fatigue and after much, and I mean much, research and encouragement from family I tried Kratom. I could not believe how much relief I had almost immediately. Now I don't take it on a daily basis, but when I am really in pain or having a flare I know that I can get relief and that is a life changer for me. In fact, a couple of weeks ago, my daughter and granddaughter wanted to go see a cave because granddaughter had never been in one. Well, I took the Kratom that morning with some orange juice and for the first time in a very very long time, I walked for over an hour down stairs, and ramps and uneven ground in a cave. Yea, I might have a life back to enjoy with the grandkids.

That was what i thought before the DEA published their intent to ban Kratom and make it a Schedule I drug. This is so wrong for so many. I hope you will take this as serious as those of us who have gotten our lives back and are functioning, stable, contributing members of society.

My name is [redacted] [redacted] and I am a mother of a 2 and a 3 year old, working at a bank and going to school full time for computer science. I was in a hit and run with a drunk driver, while I was pregnant with our son. Because of that crash, my son was born over a month early. I suffered broken ribs and many other injuries, including physical and many emotional. I couldn't function as a part of my family. With the pain and PTSD, I couldn't take care of my children, I couldn't have a relationship with my friends, or with my fiance. I lived in bed, in pain, until I was on enough prescription meds, prescribed by my doctor, to kill me. Which it nearly did. The meds only worsened my anxiety, my depression and barely worked for the pain. I thought I would be better off dead and no longer just a burden to my family. I was on (and completely addicted to) several anti-depressants, anxiety and pain meds. I had no quality of life. No way to hold down a job, school, or anything else. Finding kratom literally saved my life. I was able to get off all of the medications. My anxiety, depression, insomnia, were all gone but most importantly the severe debilitating physical pain. Was gone. I am able to function as a productive part of society, hold down a job, my family and go to school. Without kratom, none of this will be possible for me any longer. I am able to play with and take care of my kids. And contribute to my family. I feel like I am actually worth something. And I am terrified of what will happen to me, if kratom is banned. It is definitely life or death for me. Thanks for reading.

I am a registered nurse of 17 years with a bachelor degree, working on a master's. I am also a "Kratom consumer". Years ago I had a series of back injuries from lifting patients. This led to an autoimmune disorder called Ankylosing Spondylitis. A disorder that primarily attacks the spine. I have worked in various departments, from OB to ICU.

Caring for thousands of patients over the years. I tried every therapy available, from pain medication and injections, to acupuncture and herbal remedies. Nothing helped. I found myself no longer able to do my job effectively. And have had to since take a "desk job" reviewing charts. I still suffered immensely despite the biologic therapy (Humira, Remicade, and now Cosentyx) and as of last year was seriously looking into disability. Which would make me no longer a continuing member of society, and a financial burden to taxpayers. But last year I was introduced to an herb called Kratom.

I researched the plant extensively before even attempting to try it. I am personally against any recreational use of any substance and to this day have never tried a single illegal drug, even when I was young. After my research, I tried it. I found not only did it help with my pain, but I could think clearer and function better than I had in years! The worst side effect was constipation. I was able to wean off of prescribed opiates, which did help with pain but made it impossible to do my job. And as a nurse, I can not have any mind altering substances in my system while caring for patients. Since Kratom doesn't cause the drowsiness or alter my thinking process like opiates, I am now able to work better than I ever did before.

I have several other agendas. The first being that I have family that depends on this herb to function. One with an autoimmune disorder similar to mine, and several others with back injuries as a result of construction jobs and motor vehicle accidents. All have said that they cannot function well without Kratom. Not because of a dependency, but because of pain. And these are hard working individuals that have tried every other means available, including surgery and various medications. The other agenda I have, is I lost my spouse to suicide when he could not get the pain relief that was so desperately needed. We have insurance and he literally spent years trying every treatment and medication available to no avail. He despised drug use and never took illegal drugs in his life, and rarely took prescriptions. I often wonder if this herb could have saved his life. He was disabled for our entire 10 years of marriage and leaves behind a 9 year old daughter.

I'm a married 30 yr 4-year college educated, stay at home mom to 3 intelligent, healthy children. Some 10 years ago I was prescribed opiate painkillers for a chronic condition, Interstitial Cystitis (diagnosed via instillation and cystoscopy). I became physically dependent on the narcotic pain relief prescribed to me. When those became unavailable, my drug abusing husband introduced me to heroin to ward off withdrawal. I used that for a short duration, until I found out I was pregnant. I immediately told my OBGYN of the situation, and not wanting to risk a miscarriage from withdrawal, she placed me in a methadone clinic. There I stayed for 8 long encumbered years. I was a model patient; however, I became frustrated given that the dependency that led to my placement in the program lasted only a month. The clinic itself did nothing in terms of advocating for me to wean myself out of the clinic. In other words, while this was the safest course of action for my unborn child, this maintenance treatment had made my dependence far worse. The methadone sugar cravings wreaked havoc on my teeth and caused heart problems. I also had a close relative die from a methadone overdose during my own time dealing with the maintenance clinic setting. The heart problems landed me in the hospital when I had a seizure and was diagnosed with elongated QT syndrome, caused by the high dose methadone, at which point I was switched to suboxone. However, I was in a good place mentally in my life and I wished to be beholden to no one but myself. I had no desire to seek a "high", but I was still fearful of the withdrawal that I would incur from suboxone detox, so I researched and found Kratom. I am so eternally grateful that quality, Kratom-community vetted products from reputable vendors were available to me during this period. As a nearly catatonic mother and wife from the effects of the methadone and suboxone I felt as though I was nothing more than a burden to my family. Kratom use has never made me feel intoxicated, altered my perception of reality or cause me to have cravings after disuse. It did not make me high in any sense of the word; it repressed my pain, anxiety and depression with a slight energy boost like coffee without the jitters. I was human again. I stayed on Kratom daily for about six months, & I came off of Kratom completely a month ago. Now for the first time in a decade I am completely psychoactive substance free. There were some slight withdrawals associated with my Kratom detox after daily use for 6 months. Objectively, these included: chills, mild depression and anxiety, but the anxiety & depression were present before I found Kratom and after cessation. If Kratom were to remain legal, I would undoubtedly prefer to utilize Kratom tea to combat my ongoing depression and anxiety over prescription medications. I have tried many, only to stop due to the debilitating side effects I've experienced. I can only speak for myself and how Kratom has helped me become a better mom, wife and overall human being. Despite not being a current consumer of Kratom, my heart breaks for those who's livelihood and families will be torn apart from chronic pain or addiction should this DEA ban become final. My focus of advocacy sits on the heavy weight this puts on the humanity of our great Nation. The opiate epidemic is real and killing countless more everyday, when a quasi-solution is right before our eyes. This "temporary ban" is the real "imminent threat to public safety." As a once opioid dependent person, I wanted nothing more than to admit my faults and take full control mending my own physical health, while working in conjunction with my mental health professional. My heart breaks for those whose livelihood and families will be torn apart from chronic pain or addiction should this DEA ban become final. The gift of Kratom raised me out of a prescription-induced fog and dramatically increased my quality of life. This was only made possible as it was extremely effective, and more importantly, easily available, from reputable vendors for use in the privacy of my own home, with family support and supervision. Like any ingested substance, responsible use is the key and as this grassroots moment has shown, clearly, the responsible consumers far outweigh the outliers in this scenario. Please understand, I advocate for responsible Kratom use and public availability, not for me, but for the sake of the children of those suffering from the disease of addiction, chronic pain patients, anxiety/Depression/PTSD suffers, and all who will deal with the inevitable fallout from this well-intentioned but misguided decision.

I'm 65, a retired writer and horseback riding instructor. I was on hydrocodone for chronic pain since my first (of four) back surgeries in 1996, so 20 years. I learned about Kratom last year. It is the only thing other than opiates that helps this one particular kind of back pain that especially debilitates me. I have said often that finding Kratom for me was like getting released from prison. Now I will have to go back in. I don't want to live much longer that way, so I will probably check out early, especially since my fellow humans are sending me the message that they do not care that I have to live in misery. I won't. And I find myself hoping karma smites them.

A Kratom ban will not save lives, it will cost them, and mine is one of them.

[redacted] [redacted], 59, [redacted] Tx. After 15 years of relentless pain from Fibromyalgia I developed Trigeminal Neuralgia. I now have suffered from the condition known as the "Suicide" Disease (for which there is no cure) because the pain is so severe, for 10 years in addition to Fibromyalgia. Until my discovery of Kratom I was at the mercy of very serious medications that came with very serious side effects. Kratom has enabled a huge reduction in some of those medications. I no longer need to constantly take antidepressants, anti anxiety meds or strong pain killers. Kratom has enabled a intensely needed improvement in my quality of life! Never have I experienced a foggy head, "lala" land, confusion or hallucinated with Kratom like the other meds caused. I live with a deep sense of gratitude every day! Please do not take away my option of an improved life by banning Kratom!

My name is [redacted]. I am a 30 year old professional from Idaho. In 2008 I had a traumatic spine injury resulting in chronic pain. I hated taking prescription opioids for pain as they hampered my quality of life more than they helped. I found Kratom in 2012 and have taken it since with no unpleasant side effects. It has helped me with my pain, energy levels and positive outlook on life. I have reviewed all available data and I firmly believe that Kratom is as safe or safer than coffee and other caffeine containing products. Kratom should remain a supplement in the United States as it is in Canada. Many states have reviewed the available data on Kratom and decided to keep it legal. Please, focus on the problem: Prescription painkillers and illicit drugs. Kratom is not a plant that can be easily abused as it has a ceiling effect i.e. more is NOT better. Please step in to stop this regulatory overreach by the FDA and DEA. This plant is also a great tool in the fight against our current opioid problems. Kratom is NOT an opioid. This is FACT. Contrary to the statements from the DEA, Kratom has been the focus of intense study and has been found to be effective in helping people with a multitude of issues. What will they ban next? Coffee? If the DEA applied the same logic to coffee it would be a schedule 1 substance. This is a deplorable act on the part of institutions that have been entrusted to protect Americans.

My name is [redacted]. I'm a father of 5. Several years ago, I had an industrial accident and had to have my shoulder rebuilt. I was in constant pain and the doctor’s solution to that was to give me all the narcotic pain medication I wanted. After using opiates for 6 years, I had become a legal junkie. Not only was I taking the pills for pain, but also to get high. One day a friend suggested kratom. I ordered some and quit taking opiates cold turkey. 4 years later, I haven't touched an opiate and am able to successfully manage my pain with kratom. Kratom doesn't get me high, and I am not addicted, as I sometimes go a few months without taking it with no ill effects.

My name is [redacted] and I am 33 years old. I suffer from Fibromyalgia and Endometriosis. Before I found Kratom I was in so much pain from my illnesses that I would be bedridden at least 2 weeks every month. I was on 10 medications and severely depressed. The pain medications my doctor prescribed didn't really help with the pain and I became dependent on them. Seven months ago I found Kratom. Since then I have not stayed in bed one day. I am now only taking 2 medications. Kratom has helped improve my life immensely. I am no longer depressed. I even exercise now and have lost 25 pounds. My kids and husband love the person I've become and so do I.

My name is [redacted]. I am a mother and I work as a piano and violin teacher. I have been taking kratom for two years to help with pain issues. I had a prescription for pain medication before but the prescription medication left me feeling sleepy and sick for a lot of the time. When I started taking kratom it made a huge difference in my quality of life. It helps me deal with the pain (shoulder and back) and also helps with energy. I do not want to have to go back to prescription opiates. I might have to if there is a ban on kratom.

My name is [redacted] [redacted] I am 51. I have suffered from severe fibromyalgia for 10 years. I am married and have three children in college. My doctor has tried a multitude of prescriptions to help me and yet I remained bedridden. We tried Lyrica, Savella and many heavy hitter narcotics, even fentanyl, and nothing really helped. I have been to the University of Michigan hospital and the Cleveland Clinic and they couldn't find anything that could help.

Because of kratom I enjoy my family and they enjoy me. Before kratom i was chained to my bed or couch with pain and had to use a walker or wheelchair. I have been taking kratom for 2 years. Before writing this testimonial, I went on a 10+ mile bike ride with my husband. We do this pretty much everyday. Kratom isn't a cure. But now I finally have a life.

I feel like I have a sentence of death with this ban looming over me. My family and I are trying to do everything as fast as we can with events. And are doing household stuff too like putting things in easy reach as the pain will be excruciating to reach for or lift things without kratom. And tightening all stair railings as i will have to pull myself up the stairs without kratom. We have a trip to Wyoming planned for next summer with the solar eclipse. I will have to stay home and will have to find someone to stay with me should kratom be banned. I don't want to go back to being bedridden again. My family will lose me again if kratom is banned. My husband and three adult children are also fighting to keep Kratom legal.

My name is [redacted] [redacted]. I have several medical conditions which have all been GREATLY improved if not eliminated by my use of kratom. 1 Failed back syndrome 2 DDD 3 Arthritis 4 depression 5 Anxiety 6 High blood sugar 7 high blood pressure 8 Restless leg Syndrome. I have also gotten off most of my medications for these by using kratom which has helped more and with no side effects.

I was on 180 mg of Methadone for my constant pain and now I don't take anything except for kratom which manages my pain so much better. Please don't allow the DEA to ban this plant that has helped me be a productive person again. I'm now able to work part time, play and interact with my grandkids and have a normal life where before on pharmaceutical drugs I was house bound unable to do much except t for laying around in my recliner watching tv or sleeping due to the side effects of those drugs. 10 in all. I appreciate your time reading this thank you.

My name is [redacted] [redacted] I am 31 years old and I suffer from chronic migraine disorder. I have had migraines since I was a teenager but later on in my adult life they have got much worse to where I would have either a headache or migraine almost everyday of my life. I have been through countless medications (including Botox injections) and doctors to try and resolve my headaches but either would have unbearable side effects or no effect at all. I have struggled to maintain a job without getting any sick days and missing too much work that I had to be reduced to less hours. Chronic migraine is the 8th most disabling disease in America yet migraines are the most underfunded neurological disease.

I discovered Kratom after looking for other natural avenues to help my migraines since I was having no luck barely at all to resolve my pain. I researched it and decided to give it a try. I took a small dose of it and then started to see the results very fast. I have gone to having a headache/ migraine almost every day to only having a few a month. I have been able to go to work on a regular basis and get back to regular life. Kratom has helped me so tremendously and I'm afraid after it is banned I will be forced back to medication that doesn't work for me and back to pain everyday. I finally have my life back and I don't want to go back to my old life of pain and solitude. This ban can affect my life a lot and I'm scared to see it happen.

My name is [redacted] [redacted], I'm 35 years old and I'm a Cardiovascular Sonographer for a large University Hospital. I am a homeowner, tax-paying, law-abiding, professional. I'm a wife, sister, daughter, colleague, friend and neighbor and I've also been using Kratom for the last 4 years to help with depression, anxiety and to manage a past addiction to prescription painkillers. I've dealt with depression and anxiety my whole life to the point where I've been hospitalized for panic attacks. In 2009/2010 I had a few significant traumas occur in my life, one of which being my dearest friend committing suicide by putting a gun in her mouth and pulling the trigger. That was the straw that broke the camel's back as they say. At that same time I was prescribed Vicodin to treat a leg injury I had sustained and like many others I found it also assuaged the deep emotional pain and anxiety I was dealing with all day and night. When I realized I was addicted I went to my Doctor right away because I had never so much as smoked or done any substances before. He prescribed me Suboxone which was POISON for my body. I searched high and low for an alternative that would be safe, natural and not just swap one problem for another. I found Kratom and haven't touched a prescription opiate, anti-anxiety, or suboxone in four years. I'm the happiest, healthiest and most productive I've EVER been in my life and Kratom is an integral part of that. I'm afraid if this ban goes through I'll be forced to either become a felon (not an option), suffer and potentially relapse, or go back to pharmaceuticals that not only not help me but HURT me. This is LIFE and DEATH for hundreds of thousands of Americans. This plant has brought nothing but good into my life and if it's ripped away I fear for my very life.
[redacted] [redacted], BA, RDCS, RVT

My name is [redacted] & I'm a 39 year old female. In 2006 I was diagnosed with Limb-Girdle Muscular Dystrophy. On top of this, I also have chronic back pain from bulging discs, degenerative disc disease & a decade of working on an assembly line for [redacted]Co. There is no cure for my condition. Doctors prescribed me powerful narcotic pain medication to treat my pain. The side effects were terrible, so I was prescribed more medication to treat side effects. Eventually the meds stopped working. Taking the medications made me sick, but not taking them was worse. I felt hopeless in this vicious cycle & had no quality of life. Then I saw a post in my Facebook Chronic pain support group about Kratom. I did some research & placed an order. Kratom saved my life. I was able to quit taking all my pain, depression & anxiety medications. The last 514 days since I started taking Kratom I have been able to do more than I did in the previous 8 years. I feel like I've got my life back.

This is LIFE and DEATH for hundreds of thousands of Americans. This plant has brought nothing but good into my life and if it's ripped away I fear for my very life.

I am a 47 year old responsible female. I found kratom almost a year ago and have been using it daily since then to manage my chronic pain and fatigue from fibromyalgia and hypothyroidism and other chronic health issues. I was diagnosed with fibro in 2003 and was put on disability by 2004 and spent most of my days in bed. Numerous medications was tried to help with all my many symptoms but few if any really helped. Was on antidepressants, muscle relaxers, pain medicine, Fentanyl,percocet,norco,adderall,nuvigil and many others. kratom has been a lifesaver for me and has given me a better quality of life than what I have had for the last 15 years. I really don't want to go back to living my life spending all my days in bed which is really not living at all. I'm afraid that is what will happen if this amazing herb is banned, and Not just my life that will be adversely affected but thousands of others as well. Praying the ban is stopped, [redacted] [redacted]

My name is [redacted] and I'm a 40 yr old married mother of 2. I have had chronic back pain (lumbar disk degeneration, arthritic muscle spasms) since 2005. I have been on pain relievers and muscle relaxers since then. I was tired of taking pills and them not always working so I went online to find an alternative and found KRATOM! I read nothing but positive reviews about it. I immediately stopped taking pills and it's been 4 yrs now. Kratom saved my life , I am able to work full time , take walks with my family and do everyday normal activities due to Kratom. My life will be turned upside down over this DEA ban and it's not fair. I don't want to go back to pills and I won't. A natural leaf that's compared to coffee should not be banned. People should be able to take any natural remedy that they want, not the DEA telling you it's in the same class as heroin. It deeply saddens me.

My Name is [redacted]. I am 51 years old. I work as a database report writer. I have suffered my entire life from anxiety and severe depression. Anti-depressants and anti-anxiety meds have not been of any value to me as I felt little to no effect from them yet experienced severe side effects. I first tried Kratom a little over a year ago and found the effects it had finally provided some relief to both the depression and the anxiety. Everything about my health seemed to begin to balance out. I stopped consuming as much alcohol, got a healthy appetite back, slept peacefully and was generally better able to manage my life. Please reconsider the ban on a dried leaf from a tree that has saved my life.

My name is [redacted]. I have been using Kratom for chronic pain caused by the side effects from an extensive course of antibiotics for about two years, as well as gradual and long-lasting pain from complications of H-Flu Meningitis which caused me to have spinal cord damage. Before I heard about Kratom, I was taking Vicodin, but upon stopping the drug, I began to suffer extreme symptoms of withdrawal, even though my dosage was quite low. In the few weeks after stopping the Vicodin, and researching natural pain relief, I had resorted to over-the-counter pain meds such as Tylenol, Ibuprofen, and Excedrin, at one point taking as many as ten to twelve pills a day. As a result of believing I'd have to deal with this pain for the rest of my life, I was also facing depression to the point where my family started to worry. I was skeptical about Kratom, at first, but figured I'd give it a try. To date, I rarely take synthetic pain medication. Not only has Kratom provided me with wonderful pain relief, but I spend a lot less money on it compared to what I was paying for over-the-counter pain relief.

If Kratom were to become a Schedule I drug, I would have to face the real possibility of catastrophic side effects associated with prescription drugs, as well as OTCs. Knowing that Kratom provides strong pain relief without side effects gives me peace of mind that I will never have to face medical complications in the future.

I am a 61 year old female with 2 Herniated disks, Spinal Stenosis and Sciatica. I was prescribed cortisone, Xanax, Soma, and Oxycodone. I was not at all functional. Previously I had mothered 4 children (triplets are in there), and been very successful in Financial and Supplement sales since age 31. I don’t like not functioning or working. When I found Kratom I got my life back. It is very “self regulating”. If you take too much you vomit. This is about freedom of choice. We need some folks interested in Science here.

My name is [redacted]. I am 55 years old and I have been using Kratom for over 5 years. I like so many people started out using pain pills because of numerous surgeries. I searched the internet for an alternative to pain medication and found Kratom. It has been a lifesaver. Two years ago I lost my only child to alcohol. I am pretty sure without Kratom, I wouldn’t be here today. Besides helping with the pain I have, it helps me to get out of bed in the morning. The hole left in my heart is never going to go away, but with Kratom I can at least make an effort to get through another day. I don’t know what I will do if I can’t use it anymore. I do not want to be sedated for the rest of my life with pharmaceuticals just because they are legal. I prefer the natural way instead of something created in a laboratory. But I also prefer Kratom because it has worked for me.

I am a 32 year old woman with a 5 ½ year old daughter. I am an artist, musician, jewelry designer, wife, mother. I have a family history of alcoholism, and severe anxiety/depression. I also suffer from chronic back pain due to fused vertebrae in my spine. Over the years i tried several anti anxiety medications, have been addicted to opiates and a heavy drinker. My drinking got so bad that I did not foresee a day that I would be able to get through the day without a drink (or 5). I sincerely believe that if i had known about kratom sooner my drinking would not have had such a detrimental effect on my life. Nothing else has worked as well for my anxiety, for my pain, and to keep me from drinking. I don’t even like the taste of alcohol anymore. I also believe that if the several friends I knew who died from drug overdoses had known about kratom, they may still be here today. I don’t like to think about what will happen if it becomes illegal, when it helps so many people. It has truly changed my life for the better. -[redacted] [redacted], California

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My name is [redacted] [redacted] I am 28 years old and I have used Kratom for close to two years now to help with arthritis from a hip replacement as well as opiate addiction. I was in the worst place of my life two years ago before i found kratom. I had no money and no hope of escaping prescription drugs or heroin addiction. I took a title loan out on my car to get suboxone which failed me miserably I was back to narcotics within two weeks. Then I found kratom I now have a new car with money in the bank and my fiancée and I have 2 month old son. Currently I'm looking to buy a house for my family in the spring. Please don't take away my life from me and my family

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My name is [redacted] [redacted] and I am 24 years old and a graduate of [redacted] [redacted] University ([redacted]). I first started using kratom a couple of months ago for Anxiety, ADHD, and Depression. It has literally changed my life. I DO NOT use kratom to get high. I just take a 2-3 capsules 2-3 times a day and it helps my ability to focus immensely and allows me to relax and not pay so much attention to my often negative and non-productive thoughts. It is literally the only thing I’ve ever found that truly gives me relief from Generalized Anxiety Disorder. I cannot imagine this plant becoming illegal and I hate the idea of being criminalized for just trying to help myself. The only negative side effect I’ve occasionally gotten from kratom is constipation but that is nothing compared to the side effects I’ve gotten from prescription medications like klonopin (clonazepam) which has caused me to have suicidal thoughts (something I previously was never experienced with). Please, please, if you’re reading this, do whatever you can to keep this life-saving plant legal. If you don’t help and it is banned, you may deeply regret it one day when you, or someone important to you, is suffering greatly from chronic pain, anxiety, depression, PTSD, fibromyalgia, or many of the other things that kratom helps with, and you/they do not have access to this natural alternative. Thank you so much for you time. All the best, [redacted].

My name is [redacted]. I've had a problem with drugs since I was 16 years old. In and out of prison since I've been 20. I recently found out about kratom about 2 years ago. I've become a productive member of society since then. I don't ever want to get high. I finally am on the road to getting custody of my son. Before this time, I'd use everything I could get my hands on to try and maintain my addiction. Now, I don't spend every bit of my money on drugs. I exercise, hang out with friends, actually participate in my life, not just exist. There should be no reason for this plant to be banned. It helps me with social anxiety and ADHD. I've tried over prescription medications for both, and I end up grossly abusing them, and end up in that downward spiral again. I'm afraid that once I end up running out of kratom, with it being banned, I'll head right down that path again. I'm 29 years old and, for the first time in my life, have been successful. It's about to all be taken away. I can see why heroin is a scheduled drug, it destroys lives, I'm yet to find someone who had their life made WORSE by taking kratom!! - [redacted]

I am a thirty-four year old U.S. Army veteran. I have been married for over eleven years and have two children. I have been using Kratom in place of opiates the VA hospital prescribed. I do not get "high". I do feel a slight energy boost. I also feel relaxed because the pain in my back is not overwhelming. I suppose that if Kratom is made illegal I will still try to find it. So then this U.S. veteran of two tours in support of OIF will become a felon. [redacted]. [redacted]

I am a 29 year old logistics coordinator. For the past 10 years I have struggled to work because of pain, mostly in my back, but other places as well. I always thought it was because I was heavy, so I lost weight. I was still in pain. I tried to get into better shape, exercising most days of the week; gritting my teeth through body wide muscular pain. Every day. I was diagnosed with many acute conditions, many times. Pulled muscles, tendinitis, bursitis, TMJ. I went to physical therapy for my hands, my back, and my feet. I saw a chiropractor. I was placed on many medications, such as steroids, anti inflammatories, muscle relaxers, and antidepressants. Xrays showed narrowing of my spine, but nothing could explain the constant and continuous pain everywhere else. The word 'fibromyalgia' has been thrown around, but the suggested treatment is just more of the same. I was told about kratom in a back pain support group. People were always talking about their pills, usually narcotics. What symptoms get you what prescriptions, etc. It was a sad place to be. I ordered kratom, completely skeptical, out of desperation. As I stood in my bedroom, crying over a pile of laundry that I couldn't fold, I placed my first order with overnight shipping. CAN YOU IMAGINE BEING IN TOO MUCH PAIN TO FOLD A TSHIRT? Kratom has picked up where medicine left off. There was nothing else the medical profession could offer me. I'm still under medical care, and I still receive regular check ups, blood work, and occasionally physical therapy. I still have pain, but I am working and living again. I'm active. I cannot imagine going back to crying over laundry again. Its simply unimaginable to be left with a life like I was living. It wasn't worth living.
Sincerely, [redacted] [redacted], MA

I am a 35 year old female. Fitness and health is my life. I started using kratom about three months ago. It is the only substance that gets rid of my monthly menstrual cramps, it relieves severe PMS and I use it for pain management related to workouts. I also have found it to be the best substance I have ever used for anxiety, and social anxiety. I am not a drug user, I am very healthy and I run obstacle races for fun. I am currently attending grad school for herbal medicine to earn a master's degree in science. Kratom is what gave me the motivation to start this endeavor. I do not depend on kratom to live, but kratom enhances my life greatly. I am truly my best self on kratom. I am focused, determined and resilient naturally and kratom brings out the best of those qualities.

My name is [redacted] [redacted]. I'm a 46 year old Father from [redacted] [redacted] MI and I'd like to voice my concern.

Kratom has helped me control my anxiety and depression disorder to a great degree and has helped me to completely stop my use of alcohol any illicit drugs and lose 40 pounds. My doctor is impressed with my progress and the fact that my blood pressure is now in the healthy range also due to kratom use. In fact it is better than it was when I was in my 20's. My life is much more stable for myself and my children now thanks to it after over a year of responsible use. It is as safe as coffee and abuse potential is non existent, the worse that can happen if too much is taken is that you will get sick and may vomit..

Kratom is a safe alternative to pharmaceutical drugs with important medicinal uses and has changed my life, so I'm asking you to please help stop this bill. Please do not try to Schedule this drug until more research can take place, this is in no way a synthetic or dangerous substance and has safely been used by Buddhist monks for thousands of years.

Please do not fall prey to the propaganda, such as deaths and getting "high" that have been put out by Pharmaceutical companies that will lose the deadly grip they have on the American population with deadly and addictive opioids and other drugs.

My name is [redacted] [redacted]., I'm a 37 year old chronic illness/rare disease patient, a wife, daughter, sister and mother of 3. I started having life altering symptoms at the age of 18 and slowly declined over a decade before I received a correct diagnosis. At that point I was pretty much bedridden, had missed out on my young adult life, isolated myself from friends and most importantly, my husband and children missed “ME”.

My condition is endocrine so I can't choose alternatives for the bodies master hormones I must replace to stay alive. Patients with my condition are often left weak, severely fatigued, unmotivated and lacking the overall feeling of well-being. Synthetic hormones (prescription) can only do so much. Research has shown that Ritalin and antidepressants can help us. I tried many antidepressants and stimulants but didn't feel like myself and hated the side effects.

I found Kratom in 2012 and immediately felt better. I was happier, I no longer needed to nap 3 times a day, I had the strength and energy to play with my children and most importantly I felt as close my old self as I will get. I have used the same strain and dosage for at least 4 years. Without Kratom I'll end up back in bed sleeping my life away. My husband will pick up the slack, my children will miss their mom (my youngest is 15 months) and I'll have to live my life wishing others wouldn't hurt if I were just put out of my misery.

I had more faith in our government. I feel like I'm in another less fortunate country or a bad dream. Please don't take away the one thing that helps so many and harms so few (if any). I want to remain a productive member of society. I shouldn't be FORCED onto disability.

My name is [redacted] [redacted] and I am 61 years old. I am a wife, a mother, a friend, a grandmother, a Christian, and I take kratom. No one chooses to live a life in chronic pain. I am not gifted with words, as a matter of fact, my illness often makes it difficult to put my thoughts clearly. But for this life giving, gentle herb, I will attempt to tell my story.

In 1992 I thought I had suffered a work related injury. Repetitive actions lead to pain that quite often made it impossible to work. Later it was determined that I have fibromyalgia, and a host of back and neck issues. I wish I could name them all. Years of doctor visits, following every instruction the various doctors gave me from medications to massage, physical therapy, acupuncture, I was finally told there was nothing more that could be done. Everyday was, and is, one lived in pain. Until I found kratom. It was briefly mentioned in a fibromyalgia support group. Taking it has been a Godsend. With narcotics, the pain never stopped. Yet with kratom, I have days that I forget that I have these illnesses. It truly has been a miracle for me. I have always lived my life "naturally". Choosing organic foods, dietary supplements, etc. Being careful what I put in my body. I take kratom in its powdered form, mixing it with a bit of orange juice. Within moments, the pain is gone. I have no side effects with kratom, only pain relief and the thrill of living my life again. I have been able to go for walks and even hikes with my husband, cook again, clean house--simple things that most take for granted. Please help me continue to live my life productively and healthily. Please help us stop, or delay the ban on kratom in the US.

My name is [redacted] & I'm 46 years old. I've suffered from depression my entire life. At 15 I was prescribed ritalin along with prozac. By the time I reached my 21st birthday I was a full blown alcoholic addicted to a host of prescription medications. Suicidal thoughts loomed through my head daily nevermind the fact that I now had a marriage and a baby. I made countless visits to a psychiatrist and doctors only to be PRESCRIBED MORE MEDICATION THAT DID NOT WORK.
In 2005 I found myself desperate for change and I quit everything cold turkey! The next 6 years were a fog and I found myself sleeping all day with no quality of life. I found kratom through much research. The results for me taking kratom were out of bed, out of pain, and the depression was at bay finally! For the first time in my life I was happy & productive part of society. I've been taking kratom since 2011 and NOTHING ELSE! If the ban goes through I will eventually go back into a depression and be in physical and emotional pain. I vaguely remember my life without kratom but now expected to deal with the ban from a tree leaf. I don't want to go back to that life but I know myself well enough that all the old symptoms of depression will come back. Life without kratom means a life with depression because i will not go back to the men in white coats for their laboratory pills when my creator has left me a leaf to take care of all of it! My inherent right!

I'm a 51 year old woman living with Fibromyalgia, Reflex Sympathetic Dystrophy and other conditions. I use kratom for chronic pain and it gives me great relief that prescription pain meds don't offer.

I'm a 47 year old wife, Mom and Grandma. I use kratom to help with my RSD, Depression, Anxiety, insomnia, nerve pain, herniated disks, PTSD, social anxiety, muscle spasms, arthritis, chronic fatigue and regulating my blood pressure. I was on countless pharmaceuticals and endured painful injections on a regular basis and it didn't help any. With pharmaceuticals I was unable to function and became a zombie. There's about 2 ½ years that I don't remember much of because of all the meds they had me on. I started searching for an alternative that was less harmful for my body and state of mind. I've tried many things and kratom is the one that works best for me. It is the only thing that helps with the nerve pain. My overall health and state of mind improved dramatically. I have been taking kratom for over 2 ½ years now and I can't imagine life without it. It allows me to control my pain and gives me the energy to get up and moving. I sleep way better and my thought have become more positive. It doesn't leave me in a fog or high at all. It actually clears my head and allows me to function somewhat "normal". Before I found kratom I had lost all hope and the burning pain was eating me alive. I would lay curled up in ball crying and wishing for death. Kratom gave me my life back! The prospect of returning to that state is absolutely terrifying! I love where I live, my family is here. But if I lose kratom we are seriously considering moving out of the country. I shouldn't have to choose between my health and my home. I have seen kratom help people get off of dangerous drugs and regain control of their life. I have seen it help with chronic migraines, Fibromyalgia, Lyme Disease, Addiction, ADHD, depression, anxiety and so much more! And it is safe. You take too much you puke. And it tastes gross so the kids won't want to get into it and if they do, I'm confident it won't hurt them, unlike dangerous pharmaceuticals. My body responds better to plant medicine and I choose kratom. Please don't take my quality of life away by allowing this ban to go through.

My friend just got back on Adderall for anxiety because of this ban. Within a week she passed out while driving and totalled her car and got a DUI for driving on prescription medication. Kratom never did this to her

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My name is [redacted]. I am 35 year old father of two young children I work full time and live with my partner, the mother of my two children. I have been on one medication or another since I was 14. I also starting drinking and drugging around that age. I have suffered from severe depression and social anxiety as well as temporal lobe epilepsy. For many years I drank very heavily since no medication I was prescribed ever worked for me. I couldn't hold jobs, I got in trouble with the law, I was a degenerate basically. I also became addicted to opiates around the age of 21 and this led to many many years of struggling with my addiction. I was a true blue drug fiend, shooting whatever I could find into my vein and doing any substance I could get my hands on. I was a legit danger to society with no cares but to get high and get there quick. My struggle resulted in me losing both my children and my partner I ended up on the streets shooting heroin, smoking crack and suicidal. In the past two years I have been able to get off the streets, get off of all hard drugs/prescriptions got my family back together, get an apartment, get a car, thrive in my workplace (a cook at the head of a line in a very busy restaurant) and combat my depression and anxiety. Without a strong, loving and supportive partner, and Kratom, none of this would be possible. I am not willing to let this plant go without a hell of a fight. It is a life saver. And trust me IT DOESN'T GET YOU HIGH. I WOULD KNOW!

I started taking Kratom for Depression and anxiety. I was on pharmaceutical antidepressants for 25 years and still was not living a happy life. I was actually miserable and couldn't care less about life. Even with prescription drugs, I would not shower or brush my teeth, sometimes for weeks! I was beautiful yet didn't care that I was rotting in a mental prison that was physically paralyzing.

In November 2015, a friend suggested that I try Kratom to help with my depression. I can't even begin to tell you what Kratom has done for me....It has given me a life that I used to dream about, a life that never existed for me, a life that I thought I could never have! 2015/2016 has been THE BEST YEAR OF MY LIFE, I have traveled, reconnected with family and friends, began living a healthy lifestyle of Clean eating, exercise and spiritual well being! None of the prescription pills ever brought me this close to happiness. Big Pharma and Doctors have had 25 years to get it right..they FAILED ME. Now it's my turn to get it right...AND I DID!

Since word of the ban on Kratom, I decided to finish up what little bit I had in preparation for the Scheduling. I did not taper down, I did it cold turkey. I had no withdrawals, no cravings and no suffering. I'm sad to say, day 4 without Kratom. I quickly returned to my natural state, staring into space, completely disconnected, expressionless and exhausted, while being TRAPPED in the memories of such a great year and FEARING I will never experience life like that again. I do not have to live this way, I've found a plant that changes my existence for the better..This is MY LIFE THAT I'M TALKING ABOUT and IT'S IMPERATIVE THAT I'M HAPPY!

I deserve better for myself and I have found better for myself but as of October 1st 2016, I will either be a criminal or severely depressed. I ask that you consider ME and my well being when you choose to support or oppose keeping Kratom legal. Please sign the Pocan/Salmon Dear Colleague letter! -
[redacted]

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Article

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Synthetic and Receptor Signaling Explorations of the *Mitragyna* Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators

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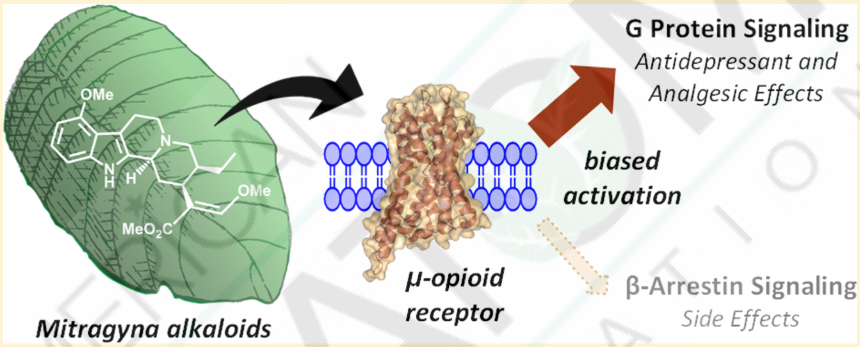
Supporting Information



ABSTRACT: Mu-opioid receptor agonists represent mainstays of pain management. However, the therapeutic use of these agents is associated with serious side effects, including potentially lethal respiratory depression. Accordingly, there is a longstanding interest in the development of new opioid analgesics with improved therapeutic profiles. The alkaloids of the Southeast Asian plant *Mitragyna speciosa*, represented by the prototypical member mitragynine, are an unusual class of opioid receptor modulators with distinct pharmacological properties. Here we describe the first receptor-level functional characterization of mitragynine and related natural alkaloids at the human mu-, kappa-, and delta-opioid receptors. These results show that mitragynine and the oxidized analogue 7-hydroxymitragynine, are partial agonists of the human mu-opioid receptor and competitive antagonists at the kappa- and delta-opioid receptors. We also show that mitragynine and 7-hydroxymitragynine are G-protein-biased agonists of the mu-opioid receptor, which do not recruit β-arrestin following receptor activation. Therefore, the *Mitragyna* alkaloid scaffold represents a novel framework for the development of functionally biased opioid modulators, which may exhibit improved therapeutic profiles. Also presented is an enantioselective total synthesis of both (−)-mitragynine and its unnatural enantiomer, (+)-mitragynine, employing a proline-catalyzed Mannich−Michael reaction sequence as the key transformation. Pharmacological evaluation of (+)-mitragynine revealed its much weaker opioid activity. Likewise, the intermediates and chemical transformations developed in the total synthesis allowed the elucidation of previously unexplored structure−activity relationships (SAR) within the *Mitragyna* scaffold. Molecular docking studies, in combination with the observed chemical SAR, suggest that *Mitragyna* alkaloids adopt a binding pose at the mu-opioid receptor that is distinct from that of classical opioids.

INTRODUCTION

The opioid receptors, and in particular, the mu-opioid receptor (MOR), are among the longest and most intensely studied molecular signaling systems in the central nervous system.[1] Likewise, the prototypical small molecule agonist of these receptors, morphine, has been used by humans as an important analgesic and recreational euphoriant since ancient times. Indeed, MOR agonists, including not only morphine itself, but also a vast number of synthetic and semisynthetic opioids, remain the gold standard of pain therapy. Unfortunately, acute MOR activation is also associated with serious side effects,

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including respiratory depression, constipation, sedation, nausea, and itching.[1,2] At sufficiently high doses, the evoked respiratory depression may be fatal. Further, the pronounced euphoria produced by MOR agonists makes them major drugs of abuse. These properties have made overdose from prescription opioid analgesics a leading cause of accidental death in the United States, killing more than 18 000 people in 2014.[3,4] Another shortcoming of MOR agonists is the rapid development of tolerance to their analgesic effects. Thus, continuing escalation of dose is required to maintain an equivalent level of pain management. Similarly, when they are abused, tolerance to the euphoric effects of opioids is also rapidly developed. Thus, in either case, chronic use often results in severe physical dependence on MOR agonists due to cellular- and circuit-level adaptations to continuous receptor stimulation. Accordingly, much effort has been dedicated to the development of new MOR agonists retaining potent analgesic effects, while mitigating or eliminating the deleterious side effects of the agents currently in use.[1−8]

Historically, MOR agonists have also been applied in the treatment of mood disorders, notably including major depressive disorder (MDD). Indeed, until the mid-20th century, low doses of opium itself were used to treat depression, and the so-called "opium cure" was purportedly quite effective.[9] With the advent of tricyclic antidepressants (TCAs) in the 1950s, however, the psychiatric use of opioids rapidly fell out of favor and has been largely dormant since, likely due to negative medical and societal perceptions stemming from their abuse potential. However, there have been scattered clinical reports (both case studies and small controlled trials) since the 1970s indicating the effectiveness of MOR agonists in treating depression. The endogenous opioid peptide β-endorphin, as well as a number of small molecules, have all been reported to rapidly and robustly improve the symptoms of MDD and/or anxiety disorders in the clinical setting, even in treatment-resistant patients.[10−17] These results have been recapitulated in rodent models, where a variety of MOR agonists show antidepressant effects.[18−21] Most recently, we have found that the atypical antidepressant tianeptine, which has been used clinically for several decades and extensively studied in rodents and other mammalian species, is an MOR agonist, suggesting that this agent exerts its antidepressant effects via direct MOR activation.[22] When taken together, this body of work establishes a clear precedent for the effectiveness of MOR agonists in the treatment of depression and anxiety. Unfortunately, the treatment of mood disorders with conventional MOR agonists is expected to suffer from the same liabilities as their use in the context of pain management. Accordingly, our laboratories have been concerned with the exploration of structurally and pharmacologically distinct classes of MOR agonists, with the aim of developing new opioid-based treatments for mood disorders and pain, which lack the classical side effects of these agents.

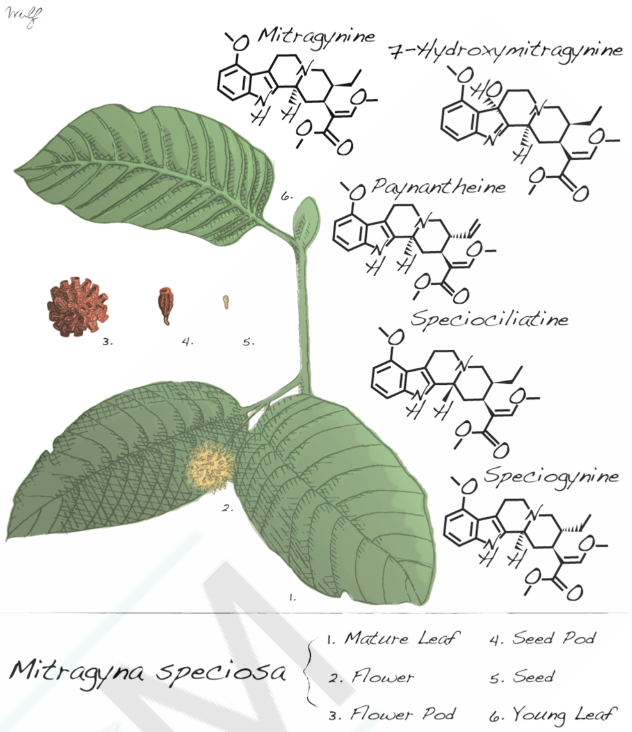


Figure 1. Leaves and fruiting bodies of *Mitragyna speciosa* and chemical structures of notable alkaloids.

It was in this context that we became interested in the psychoactive plant *Mitragyna speciosa* (Figure 1), known as "kratom" in Thailand, or "biak biak" in Malaysia, a substance that has been used by humans in Southeast Asia for centuries to treat a variety of ailments. The plant material is typically consumed as a tea or chewed directly. At low doses, kratom is primarily used for its stimulating effects. At higher doses, opioid-like effects predominate, and the plant has been used as a general analgesic and as a substitute for opium or to treat opium withdrawal symptoms. Other medicinal applications are also known, including use as a treatment for fever, cough, diarrhea, and depression. There is also a precedent for recreational use of the plant, a fact that has contributed to legal control of *Mitragyna speciosa* in both Thailand and Malaysia, but the plant remains uncontrolled outside its endemic regions.[23−27]

In light of its well documented medicinal properties, the molecular constituents of *Mitragyna speciosa* responsible for its psychoactive effects have been studied, with more than 20 unique indole alkaloids having been identified in the plant.[23−25,28] The indole alkaloid mitragynine (Figure 1) has been universally cited as the primary alkaloid constituent of *Mitragyna speciosa*, accounting for up to 66% by mass of crude alkaloid extracts.[23] The other major alkaloids in the plant have been found to include paynantheine, speciogynine, and speciociliatine (Figure 1).[23] The quantities of these major alkaloids, along with a wide variety of minor alkaloids, are considerably varied among different regional varieties of the plant and also depend on plant age, facts that considerably complicate the interpretation of reported psychoactive effects from the raw plant material.[23−25,28] Among the minor alkaloids, the oxidized derivative 7-hydroxymitragynine (7-OH)[29] (Figure 1) is of particular interest, as it has been reported to induce analgesic effects mediated through agonist activity at the MOR, exceeding in potency those of the prototypical opioid agonist morphine.[27,30]

The mechanism of action of *Mitragyna* alkaloids has also been studied both in vitro and in vivo. In particular, Takayama and co-workers have accumulated a large body of evidence implicating the opioid receptor system as the primary mediator of the psychoactive effects of these alkaloids. Specifically, both mitragynine and 7-OH exhibit nanomolar binding affinities for the MOR and possess functional activity in tissue assays.[27,30] Likewise, the antinociceptive effects of mitragynine and 7-OH in several rodent models are also inhibited by naloxone.[27,30,31] Despite this evidence for the involvement of opioid receptor systems, and specifically MOR, in mediating the analgesic effects of *Mitragyna* alkaloids, there are conflicting reports in the literature. Most notably, an early study with mitragynine indicated that the behavioral effects in cats, and analgesic effects in rats, were not reversed by treatment with nalorphine, an opioid antagonist, while at the same time, mitragynine was found to produce markedly less respiratory depression than codeine.[32] Mitragynine has been shown to bind in some degree to several non-opioid CNS receptors, including alpha-2 adrenergic receptor (α2R), adenosine A_{2a}, dopamine D_2, and the serotonin receptors 5-HT_{2C} and 5-HT_7, but the strength of these interactions has not been reported.[33] Mitragynine analgesia has also been shown to be inhibited by the α2R antagonist idazoxan and by the nonspecific serotonin antagonist cyproheptadine.[34]

Considering the many possible confounding factors present at the tissue or system level, such in vivo and ex vivo tissue assays are not ideal for confirmation of a functional effect at a particular receptor. Although receptor-level functional activity studies ([^{35}S]GTPγS binding) using cloned opioid receptors have recently been reported for several synthetic oxidized analogues,[35] no similar functional studies have been reported for mitragynine itself, or for other naturally occurring alkaloids in *Mitragyna speciosa*.[36] Given the unique and still unclear molecular pharmacology surrounding *Mitragyna* alkaloids, we undertook a thorough examination of mitragynine and a number of natural and novel analogues at the opioid receptors, measuring receptor activation and intracellular signaling.

■ RESULTS AND DISCUSSION

Mitragynine is a Partial Agonist of Human MOR. We isolated the four major alkaloids (Figure 1) from the Thai strain of *Mitragyna speciosa* and prepared 7-OH by photochemical oxidation of mitragynine (Scheme S1). Interestingly, only trace quantities of 7-OH were observed (by mass spectrometry) in our extractions of the raw plant material, and it was not possible to isolate any measurable quantity of this derivative. Therefore, it is doubtful that this alkaloid is a universal constituent of all *Mitragyna speciosa* preparations and is unlikely to generally account for the psychoactive properties of this plant.

We then set out to evaluate the activity of these compounds in HEK cells expressing the MOR, delta-opioid receptor (DOR), or kappa-opioid receptor (KOR) using bioluminescence resonance energy transfer (BRET) functional assays. In these G protein-dependent assays, the G_α subunit is fused with a luciferase (RLuc8) donor, and the G_γ subunit is fused with a fluorescent protein (mVenus) acceptor. Thus, on receptor activation, the G protein subunits move apart and the observed BRET signal decreases (Figure 2A).

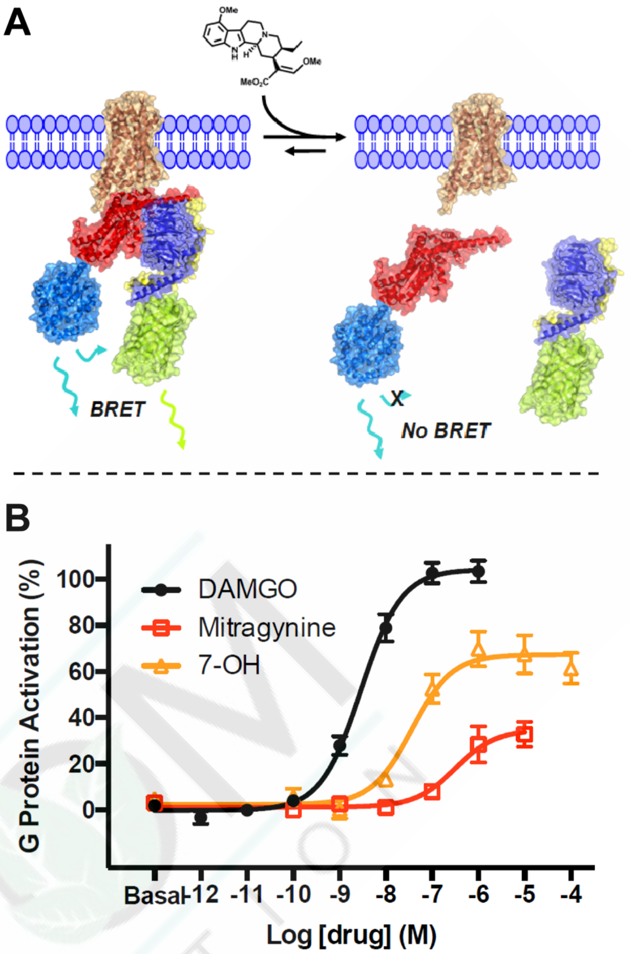


Figure 2. Activity of mitragynine and 7-hydroxymitragynine (7-OH) at the human mu-opioid receptor (hMOR). (A) Conceptual representation of the G protein BRET assay employing atomistic cartoons derived from available X-ray crystal structures. To measure G protein activation, hMOR[37] (brown) was coexpressed with $G\alpha o_B$[38] (red) fused to RLuc8[39] (teal), β1[38] (blue), and mVenus[40] (yellow-green) fused to γ2[38] (yellow). (B) Agonist activity at hMOR; positive control = [D-Ala^2, *N*-Me-Phe^4, Gly-ol^5]-enkephalin (DAMGO); curves represent the average of $n \geq 3$, with error bars representing ± SEM.

Table 1. Functional Activity of *Mitragyna* Alkaloids at Human Opioid Receptors as Determined in G Protein BRET Assays

	EC_{50} ± SEM (E_{max})[a] or [IC_{50} ± SEM (pA_2)][b] (μM)		
compound	hMOR	hKOR	hDOR
mitragynine	0.339 ± 0.178 (34%)	[8.5 ± 7.6 (1.4)]	[>10]
paynantheine	[2.2 ± 10]	[>10]	[>10]
speciogynine	[5.7 ± 2.8]	[>10]	[>10]
speciociliatine	[4.2 ± 1.6]	[>10]	[>10]
7-OH	0.0345 ± 0.0045 (47%)	[7.9 ± 3.7 (0.49)]	[>10]

[a] Agonist activity indicated by EC_{50} values, maximal efficacy (E_{max}) relative to DAMGO in parentheses. [b] Antagonist activity indicated by IC_{50} values for inhibition of a reference agonist, pA_2 determined from Schild analysis in parentheses; All data points represent mean ± SEM (μM) of $n \geq 3$.

At the human opioid receptors (hMOR, hKOR, and hDOR), mitragynine acted as a partial agonist at hMOR (Table 1 and Figure 2B, EC_{50} = 339 ± 178 nM; maximal efficacy (E_{max}) = 34%). This result represents the first demonstration of functional opioid agonist activity at human receptors with a natural *Mitragyna* alkaloid, all prior functional studies having been conducted in vivo in rodents or ex vivo in rodent tissue. In contrast, at hKOR, mitragynine was a competitive antagonist (Table 1, IC_{50} = 8.5 ± 7.6 μM; pA_2 = 1.4 ± 0.40 μM, and Figures S2 and S4), fully inhibiting the activity of the reference agonist U-50,488. Similarly, mitragynine acted as an antagonist at hDOR, but with very low potency (Figure S3). The other major natural alkaloids paynantheine, speciogynine, and speciociliatine, showed no measurable agonist activity at any of the human opioid receptors at concentrations up to 100 μM, and only weak antagonist effects were observed (Table 1 and

Figures S1, S2, and S3). The oxidized analogue, 7-OH, was also characterized and found to be a potent, partial agonist at hMOR (Table 1 and Figure 2B, EC_{50} = 34.5 ± 4.5 nM; E_{max} = 47%). Further, it acted as a competitive antagonist at both hKOR (Table 1, IC_{50} = 7.9 ± 3.7 μM; pA_2 = 490 ± 131 nM, and Figures S2 and S5) and hDOR (Table 1, IC_{50} > 10 μM, and Figure S3). The partial agonist activity of mitragynine and 7-OH at the human receptors was further confirmed in antagonist experiments, as both compounds were able to partially inhibit the response elicited by the full agonist [D-Ala^2, *N*-Me-Phe^4, Gly-ol^5]-enkephalin (DAMGO) (Figure S1).

In order to further confirm the opioid activity of the *Mitragyna* alkaloids, we performed radioligand binding studies to assess the affinity of the natural alkaloids and 7-OH for the opioid receptors (Table 2). As expected from their activity in our functional assays, both mitragynine and 7-OH exhibited significant binding affinities for hMOR. Similarly, the other natural alkaloids also bound to hMOR, consistent with their antagonist activity in the functional assays. Binding was also observed for mitragynine and 7-OH at hKOR and hDOR, again in agreement with the results of the functional assays. Further, the K_i values determined in the binding experiments were in accord with the EC_{50} and IC_{50} (after correction by Cheng–Prusoff equation) values determined in the functional experiments, or with the pA_2 values (an estimate of K_d) determined by Schild analysis. Similar binding results were also obtained at the mouse opioid receptors (Table S2). Further, our binding data with 7-OH was consistent with previous literature reports (using guinea pig brain homogenates), but the affinities determined for mitragynine at MOR and DOR were much weaker than previously described.[27,30] Given the better agreement between our in vitro data and the relative potencies of mitragynine and 7-OH in vivo, this new data may be more reliable. Taken together, the functional and binding results provide a rigorous and internally consistent assessment of the in vitro activity of the *Mitragyna* alkaloids at all three human opioid receptors.

Table 2. Binding Affinities of *Mitragyna* Alkaloids at Human Opioid Receptors

	K_i ± SEM (μM)[a]		
compound	hMOR	hKOR	hDOR
mitragynine	0.233 ± 0.048	0.772 ± 0.207	>10
paynantheine	0.410 ± 0.152	2.56 ± 0.37	>10
speciogynine	0.728 ± 0.061	3.20 ± 0.36	>10
speciociliatine	0.560 ± 0.168	0.329 ± 0.112	>10
7-OH	0.047 ± 0.018	0.188 ± 0.038	0.219 ± 0.041

[a] All data points represent mean ± SEM (μM) of $n \geq 3$.

Surprisingly, analogous assays using rodent receptors (mouse or rat) revealed that mitragynine exhibited no agonist activity, and it was instead found to act as a competitive antagonist at mouse MOR (mMOR) (Figure S6 and Table S1, IC_{50} = 1.1 μM; pA_2 = 807 ± 573 nM), fully inhibiting the activation induced by the reference agonist DAMGO. The other isolated natural products, paynantheine, speciogynine, and speciociliatine, showed no notable agonist or antagonist activity at any of the rodent opioid receptors. In contrast, the activity of 7-OH was similar at the rodent receptors (Figure S6 and Table S1). These observations complicate the interpretation of prior reports of analgesic effects elicited by mitragynine in rodent models. Further, this interspecies variation may present significant challenges in the development of compounds in this class as novel therapeutics, as activity in rodent models may not be easily translatable to humans. In this regard, it is fortunate that the more potent derivative, 7-OH, retains its agonist activity at mMOR, as the oxidized scaffold represents a more promising starting point for the development of analgesics in this class. With respect to mitragynine, it is also conceivable that the in vitro assays used in our study do not exactly replicate the receptor activation and signaling in native murine brain tissue. For example, a low efficacy partial agonist in the brain may appear as an antagonist in the cell-based assays. Thus, consideration of both interspecies and interassay differences is advised for the future development of these compounds.

***Mitragyna* Alkaloids Bias Intracellular Signaling Toward G Proteins.** Functionally selective (biased) agonists of the opioid receptors, which preferentially activate only certain downstream signaling pathways, hold promise as analgesics or antidepressants with reduced side effects. Given this potential to separate the well established therapeutic benefits of MOR activation from negative side effects, the study of functionally selective MOR ligands is a very active area of research at present.[41−44] In particular, some evidence indicates that MOR agonists biased toward G protein signaling over β-arrestin signaling display less respiratory depression, tolerance development, and constipation, while remaining potent analgesics.[45−48] Therefore, we were interested in exploring the potential for mitragynine's unique molecular scaffold to serve as a starting point for the development of biased MOR agonists. To assess the level of β-arrestin recruitment induced by *Mitragyna* alkaloids, we employed a recently described BRET assay in transfected HEK cells, which was adapted for use with the opioid receptors.[49] In this assay, the unlabeled receptor (in this case hMOR) is transfected alongside β-arrestin-2 (arrestin-3), fused with luciferase (RLuc8) and an SH3 binding domain (Sp1), and the membrane protein GAP43, fused with a fluorescent protein (citrine) and an SH3 domain. Accordingly, when an agonist induces β-arrestin recruitment to MOR, the Sp1 domain on β-arrestin is brought into proximity with the membrane-localized SH3 domain and an interaction occurs. This results in concomitant association of the luciferase donor and fluorescent protein acceptor, and a BRET signal is observed (Figure 3A). An advantage of this format is that native receptor can be used, avoiding potential confounds related to C-terminal tagging on expression or function.

As measured in this cell signaling assay, DAMGO induced robust recruitment of β-arrestin. Interestingly, both mitragynine and 7-OH were found to elicit no measurable β-arrestin binding, even in the presence of G protein-coupled receptor kinase 2 (GRK2), which typically enhances coupling to β-arrestin (Figure 3B). Because of this extremely weak signal, we were not able to quantitate the magnitude of functional selectivity for mitragynine and 7-OH. However, since both compounds exhibit significant efficacy for activation in the G protein dissociation assay (Figure 2), there is a strong qualitative bias in favor of G protein signaling in these cells. Such selectivity for G protein-dependent signaling may explain the reduced respiratory depression previously reported for mitragynine compared to codeine,[32] although any such connection between upstream receptor signaling and physiological properties must be considered speculative. In any case, both mitragynine and 7-OH trigger downstream signaling

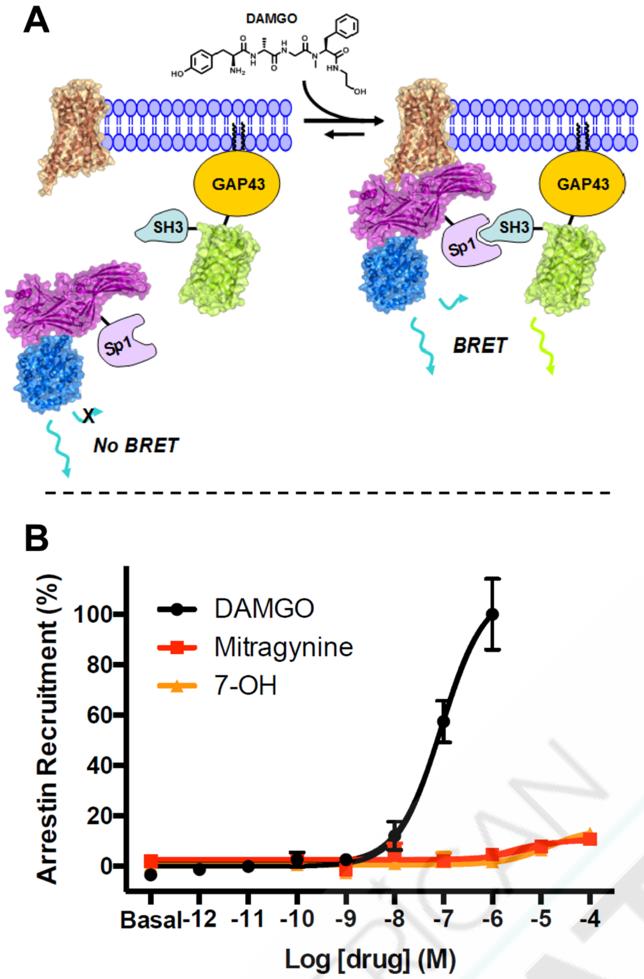


Figure 3. Mitragynine and 7-OH do not recruit β-arrestin. (A) Conceptual representation of the β-arrestin BRET assay employing atomistic cartoons derived from available X-ray crystal structures. To measure β-arrestin recruitment, hMOR[37] (brown) was coexpressed with β-arrestin-2[50] (purple) fused to RLuc8[39] (teal) and Sp1, GAP43 fused to citrine[40] (yellow-green) and SH3, and G protein-coupled receptor kinase 2 (GRK2). On β-arrestin recruitment, association of the Sp1 and SH3 domains results in an increase in the BRET signal between RLuc8 and citrine. (B) β-arrestin recruitment at hMOR, positive control = DAMGO; curves represent the average of $n \geq 3$, with error bars representing ± SEM.

significantly different from that induced by DAMGO. These results provide a good rationale for future experiments aimed at examining cellular signaling in relevant neuronal cells and mapping the effects of structural modifications on the level of functional selectivity.

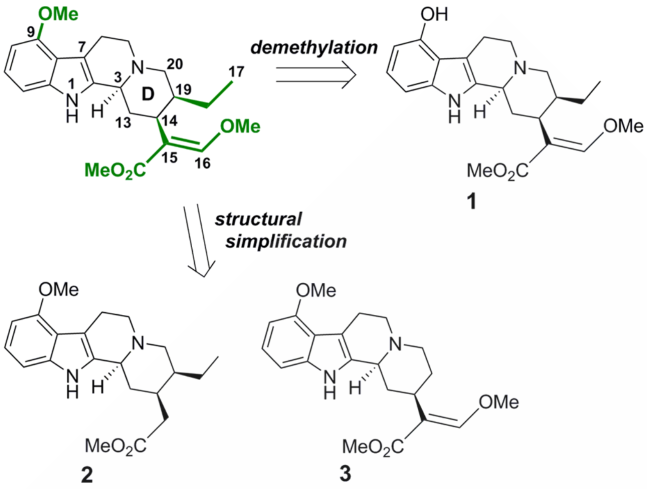


Figure 4. Key SAR locants of *Mitragyna* alkaloids (highlighted in green) and select analogues designed to interrogate each position.

SAR Exploration: Strategy. Having confirmed the MOR agonist activity of both mitragynine and 7-OH, we chose to explore several key structure–activity relationships (SAR) within this scaffold. In particular, we were interested in the effects of modifications at three positions: the methoxy group at position 9, the ethyl group on ring D, and the β-methoxyacrylate moiety (Figure 4). The aryl methoxy group at position 9 was of particular interest, as in the classical morphinan and benzomorphan opioid scaffolds, the change from aryl methoxy to phenol at key position 3 (e.g., codeine to morphine), typically results in a dramatic increase in potency. Likewise, unsubstituted phenyl analogues in these scaffolds also exhibit weak activity.[51] The importance of a phenolic moiety in many known MOR ligands is proposed to be due to formation of a water-mediated hydrogen bonding network with H297$^{6.52}$ (superscript numbers refer to Ballesteros and Weinstein's generic numbering scheme[52]), as shown in two recent X-ray crystal structures of MOR.[37,53] Accordingly, it was hypothesized that if mitragynine binds in a similar pose, then the corresponding desmethyl analogue **1** (Figure 4) would be expected to exhibit significantly increased potency. We also envisioned simplification of the D ring substituents by selective deletion of the enol ether (**2**) or pendant ethyl group (**3**) (Figure 4), analogues which would probe previously unexplored SAR in this region.

Enantioselective Total Synthesis of Mitragynine and Analogues. Although 7-OH and the desmethyl derivative **1** were prepared from the isolated natural product (Scheme S1), we also desired a total synthesis of mitragynine that would allow for the construction of more extensively modified analogues. Accordingly, we envisioned a synthesis starting from 4-methoxyindole, where ring C could be installed via a Bischler-Napieralski reaction to give a 3,4-dihydro-β-carboline. This intermediate would then be subjected to an enantioselective, proline-catalyzed Mannich–Michael-type cyclization with the appropriate enone to install ring D and set the stereocenter at position 3. This transformation was developed by Itoh and co-workers, and has been successfully employed in the total synthesis of several structurally similar indole alkaloids.[54−56] The resulting tetracyclic ketone would serve as a versatile intermediate for the synthesis of a variety of analogues, including mitragynine itself (Figure 5).

The required 3,4-dihydro-β-carboline (**4**) was successfully prepared in a six step sequence starting from commercially available 4-methoxyindole (21% overall yield, Scheme S2A). The required enone (**5**) was synthesized from methyl 2-ethyl-3-oxobutanoate according to previously described procedures (Scheme S2B).[57]

With the necessary building blocks in hand, we attempted the key proline-mediated step for formation of ring D. Initial experiments with crude β-carboline **4** treated with an excess of enone **5** in the presence of proline, afforded the desired ketones in moderate yield as a mixture of epimers **6** and **7**. Importantly, we found that the major diastereomer **6** was obtained in high enantiomeric excess (*ee*), while the minor diastereomer **7** was obtained in much lower *ee*. After optimization of the reaction

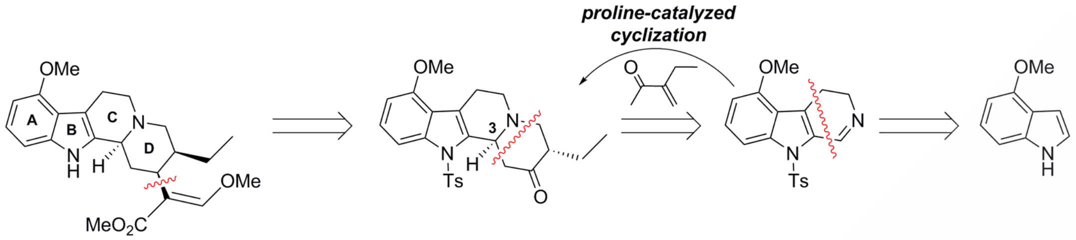
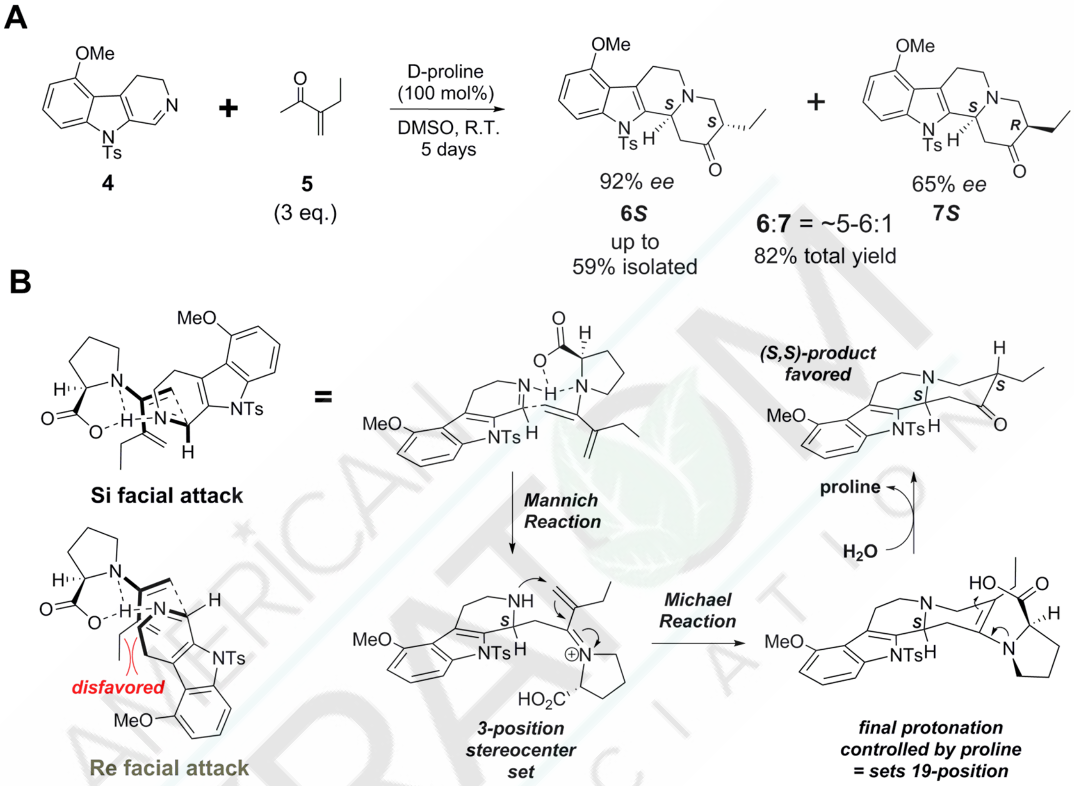


Figure 5. Retrosynthesis of mitragynine.

Scheme 1. Stereoselective Formation of D-Ring

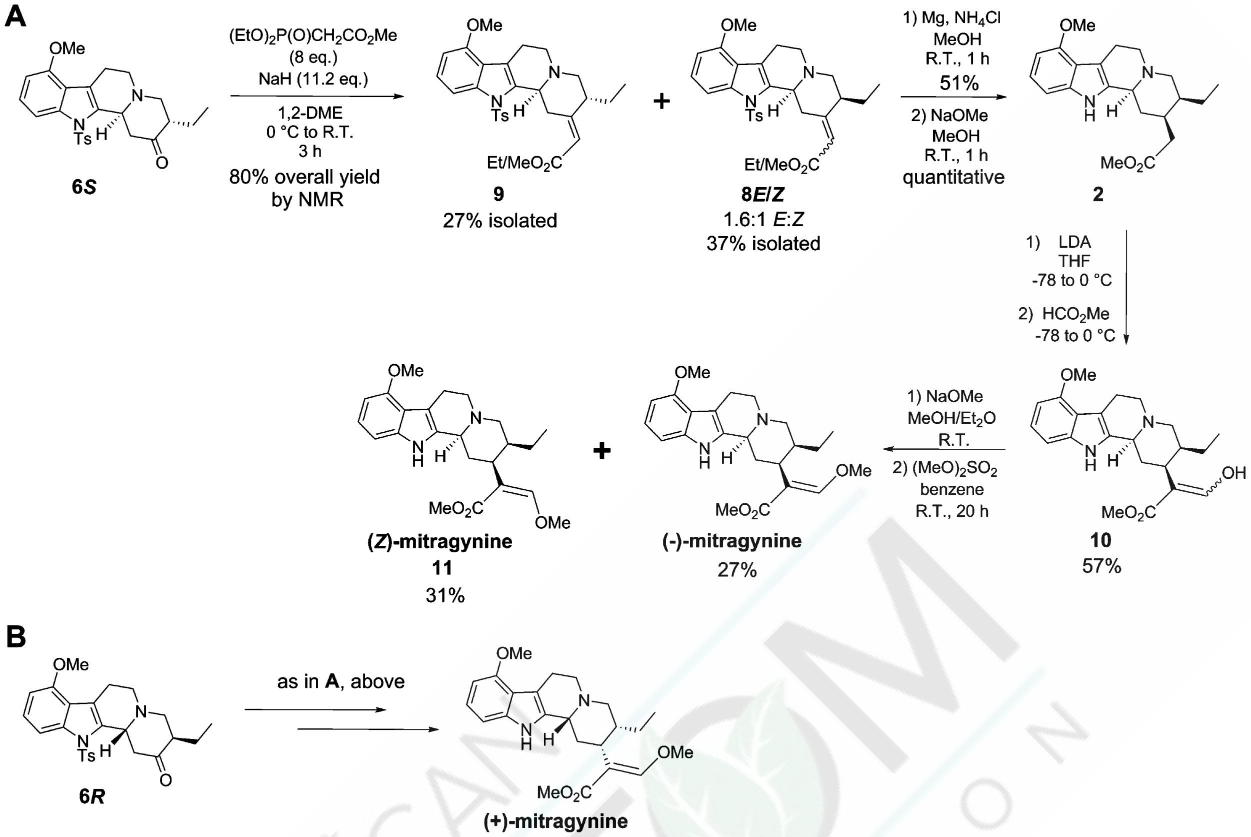


conditions (it proved crucial to purify the β-carboline by chromatography), the desired ketone isomer **6*S*** could be obtained in good yield and excellent enantiomeric excess (Scheme 1A). To rationalize the stereoselectivity of this transformation, a two step mechanism (Scheme 1**B**, D-proline shown) can be imagined, in which a Mannich-like reaction between the proline enamine of enone **5** and the β-carboline **4**, first sets the stereocenter at position 3. This is followed by intramolecular Michael addition to close the ring. In the last step, proline controls the face of protonation during hydrolysis, thereby also influencing the stereocenter at position 19. Proline is believed to be involved in control of the stereochemistry at the 19-position, as the diastereomeric ratio obtained in the reaction varies, and is different from that observed when either ketone product (**6** or **7**) is epimerized under basic conditions. Thus, the orientation of this stereocenter is not due simply to thermodynamic equilibration of the ketone product.

With key intermediate ketone **6*S*** in hand, the next challenge of the synthesis was to effect epimerization of the pendant ethyl group into the appropriate β stereochemical configuration (as in mitragynine). This could not be accomplished by thermodynamic equilibration of the ketone with base or acid, as the desired stereochemistry positions the ethyl group in the less favorable axial configuration. As an alternative strategy, we envisioned that pseudoallylic strain in the ene-ester product of a Horner−Wadsworth−Emmons (HWE) reaction, or in the corresponding transition state, might be used to perturb the equilibrium away from the equatorial alignment.[58] Therefore, ketone **6*S*** was treated with the carbanion formed from methyl diethylphosphonoacetate, and partial epimerization was indeed observed (Scheme 2A). The ene-ester with the desired axial ethyl group was obtained as a mixture of *E* and *Z* isomers, **8*E*** and **8*Z*** (55 mol % of total product by NMR), while the ene-ester with retention of configuration at the ethyl group, **9**, was obtained exclusively as the *E* isomer (45 mol % of total product by NMR). Unfortunately, the low reactivity of ketone **6*S*** necessitated the use of large excesses of phosphonoaceate, a requirement that led to partial transesterification of the methyl ester (products **8** and **9** contained ~25 mol % of the corresponding ethyl ester).

With the ethyl group successfully epimerized to the appropriate position, the mixed ene-esters **8*E*/*Z*** were converted to (−)-mitragynine by a sequence of several key steps, including the simultaneous reduction of the ene-ester and detosylation with magnesium, transesterification, Claisen condensation (formylation), and *O*-methylation[59] of the enol-

Scheme 2. Total Synthesis of Mitragynine in Both Enantiomeric Forms



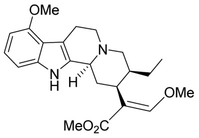
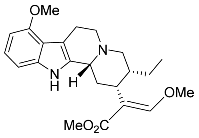
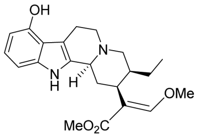
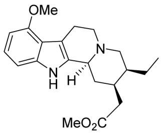
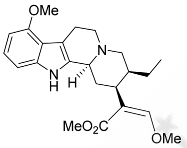
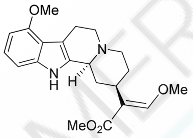
ester intermediate **10** (Scheme 2A). The final *O*-methylation step provided both (−)-mitragynine and the isomeric analogue (*Z*)-mitragynine (**11**) in modest yields. Starting from ketone **6*R*** and employing the same synthetic sequence, the unnatural enantiomer, (+)-mitragynine, was also obtained (Scheme 2B). Comparison of this material to the natural product by chiral HPLC confirmed their opposite stereochemistry, and thus, the absolute stereochemistry of the ketone products **6** and **7** obtained in the proline-catalyzed cyclization.

Synthesis of Desethylmitragynine. Considering that speciogynine, which is epimeric with mitragynine at the pendant ethyl group on ring D, was inactive as an opioid agonist in vitro, we reasoned that the nature and orientation of the substituent at this position was important for activity, and thus decided to further define the tolerance of the scaffold in this region via synthesis of the desethylmitragynine analogue **3** (Figure 4). This dramatically modified analogue was prepared by a synthetic sequence analogous to that applied for the synthesis of mitragynine, starting with the treatment of *β*-carboline **4** with methyl vinyl ketone in the presence of D-proline (Scheme S3).

Opioid Activity of Synthetic Analogues. With a variety of semi- and fully synthetic mitragynine derivatives in hand, key SAR of this molecular scaffold at the opioid receptors could be further explored. In particular, the synthesized analogues allowed investigation of the key moieties highlighted above, namely the aryl methoxy group at position 9, the *β*-methoxyacrylate moiety, and the ethyl group on ring D (see above, SAR Exploration: Strategy), as well as the importance of the absolute stereochemistry. As expected, the unnatural enantiomer (+)-mitragynine was found to be a much weaker agonist at hMOR, in terms of both potency and maximal efficacy (Table 3). Surprisingly, however, in contrast to naturally occurring (−)-mitragynine, it was found to be a low potency partial agonist at hKOR ($EC_{50} = 9.1 \pm 4.3\ \mu M$; $E_{max} = 31\%$). Apparently, inversion of the stereochemistry in this scaffold is sufficient to switch from antagonist to agonist activity at hKOR.

In examining the specific functional groups identified above (Figure 4), we observed several important trends. For one, the switch from a methoxy group to a hydroxy group at position 9 had very little effect on activity at hMOR, with the phenolic analogue **1** being of similar potency and efficacy to mitragynine itself (Table 3). This result suggests that the mitragynine scaffold is likely to adopt a unique binding pose compared to classical morphinan- and benzomorphan-derived opioids, which display a dramatic relationship between their MOR activity and an exposed phenol group. Moving to the *β*-methoxyacrylate moiety, removal of the enol ether, as in the total synthesis intermediate **2**, completely eliminated activity at hMOR (both agonist and antagonist). In contrast, the very close analogue (*Z*)-mitragynine (**11**), was found to possess very similar activity to the natural product, indicating that stereochemical inversion of the *β*-methoxyacrylate moiety is tolerated (Table 3). Lastly, we turned our attention to the ethyl group on ring D. Results with speciogynine (Table 1) had already demonstrated that epimerization of this group was sufficient to switch from agonist to antagonist activity at hMOR, while also reducing binding affinity (see above, Tables 1 and 2, mitragynine vs speciogynine). Examining the desethylmitragynine analogue **3**, we found that this derivative retained agonist activity at hMOR, but with much lower potency (Table 3). Thus, the substituent at position 19 is important for controlling both efficacy (agonist vs antagonist) and potency. The synthetic derivatives described

Table 3. Agonist Activity of Synthetic Analogues at hMOR as Determined in G Protein BRET Assays

Compound	*Structure*	*EC_{50} ± SEM (% efficacy) (μM)*[a]
(-)-mitragynine		**0.339 ± 0.178 (34%)**
(+)-mitragynine		**3.34 ± 1.1 (18%)**
1		**0.681 ± 0.379 (29%)**
2		**>50**
11		**0.219 ± 0.071 (38%)**
3		**12 ± 7.6 (59%)**

[a] Agonist activity at hMOR indicated by EC_{50} values, maximal efficacy (E_{max}) relative to DAMGO in parentheses; All data points represent mean ± SEM (μM) of $n \geq 3$.

here ((+)-mitragynine, **1**, **2**, **3**, and **11**) were also found to be without activity at hKOR and hDOR (agonist and antagonist mode, EC_{50} and IC_{50} both >30 μM).

Molecular Docking Reveals a Unique Binding Pose. In order to rationalize our empirical SAR observations in the mitragynine scaffold and inform future rational design, we conducted preliminary molecular docking studies. Specifically, AutoDock[60] was used to dock mitragynine and several of the analogues described above in the binding pocket of the agonist-bound X-ray crystal structure of mMOR (PDBID = 5C1M)[37] (Figure 6).

The top-scored binding pose of (−)-mitragynine in the orthosteric site of the receptor partially overlapped with the binding pose of the cocrystallized morphinan-derived agonist, BU72, but exhibited some dramatic differences (compare Figure 6A to Figure S7). Although (−)-mitragynine and BU72 share a polar interaction between their protonated amines and D147$^{3.32}$, which is well-known to be critical for the binding of classical opioid agonists and antagonists,[37,53] other important ligand−receptor contacts are significantly different. In BU72 (Figure S7), the phenol occupies a hydrophobic pocket formed by TM5 and TM6 and forms a water-mediated hydrogen bonding network with H297$^{6.52}$, an interaction that is common to opioid ligands in the morphinan class (see above for discussion, SAR Exploration: Strategy).[37,51,53] In contrast, our docking studies suggest that the methoxyindole domain of (−)-mitragynine is preferentially directed toward an alternative hydrophobic pocket formed by residues of TM2 and TM3 (Figure 6A), which appears to lack a means for forming an analogous hydrogen bonding network. This result is in agreement with the minimal activity difference observed in vitro between (−)-mitragynine and phenolic derivative **1** (Table 3). Instead, the enol ether domain (part of the β-methoxyacrylate) of mitragynine appears to be directed into the same region as the phenol of BU72 (toward TM5 and TM6). Thus, it can be speculated that this functional group participates in an analogous hydrogen bonding network with H297$^{6.52}$, consistent with the complete loss of activity when this group was removed (see compound **2**, Table 3).

The importance of the ethyl group on ring D is also explained by the predicted lowest-energy binding pose of (−)-mitragynine. In comparing the orientation of this ligand with that of BU72 (Figure 6A and Figure S7, respectively), it can be seen that the ethyl group occupies a nearly identical region as the *N*-methyl group of BU72, being in the vicinity of several hydrophobic residues (M151$^{3.36}$, Y148$^{3.33}$, and Y326$^{7.43}$). Accordingly, loss of this group, as in compound **3**, would be expected to diminish hydrophobic ligand−receptor interactions and reduce activity, as was observed (Table 3).

Docking of other mitragynine analogues described above also produced results that were in agreement with the in vitro activity data. For example, in accord with its similar in vitro activity to (−)-mitragynine, (*Z*)-mitragynine (**11**) adopted a nearly identical binding pose (Figure 6B). Likewise, the predicted low-energy binding pose of 7-OH was also similar, with all key functionalities (the acrylate, ethyl group, tertiary amine, and indole) occupying very similar positions (Figure 6C). Interestingly, the 7-position hydroxy group does not appear to make a close contact with the receptor surface, and thus, potential hydrogen bonding interactions do not seem to be involved in the significant increase in potency afforded by oxidation at position 7. Instead, the slight bend introduced to the core structure by this modification appears to be more important. Notably, while (−)-mitragynine interacts with W293$^{6.48}$ through its acrylate group, 7-OH interacts with this residue through both ethyl and acrylate groups, according to the chosen cutoff for apolar interactions (4.5 Å between heavy atoms; see Table S3). In contrast, docking of the unnatural enantiomer, (+)-mitragynine, revealed a dramatically different binding pose, reversed in its overall orientation in the pocket (i.e., with the acrylate projecting toward TM2 and TM3, see Figure S8A and compare with Figure 6A), in agreement with its weak activity in the functional assays.

We also docked paynantheine, speciogynine, and speciociliatine, compounds which bind to hMOR, but exhibit no agonist activity, instead serving as competitive antagonists. Considering paynantheine and speciogynine, the inverted stereochemistry at position 19 (vinyl or ethyl group) induces a significant shift of the indole moiety toward TM1 and away from TM3 (Figure 6D), which results in the formation of additional contacts with TM1 (Y75$^{1.39}$) and TM6 (H319$^{7.36}$) that are not seen in the docking of the active compounds. Moreover, the hydrophobic interactions between the indole methoxy group and V143$^{3.28}$ and I144$^{3.29}$ observed with (−)mitragynine are lost in these analogues, potentially resulting

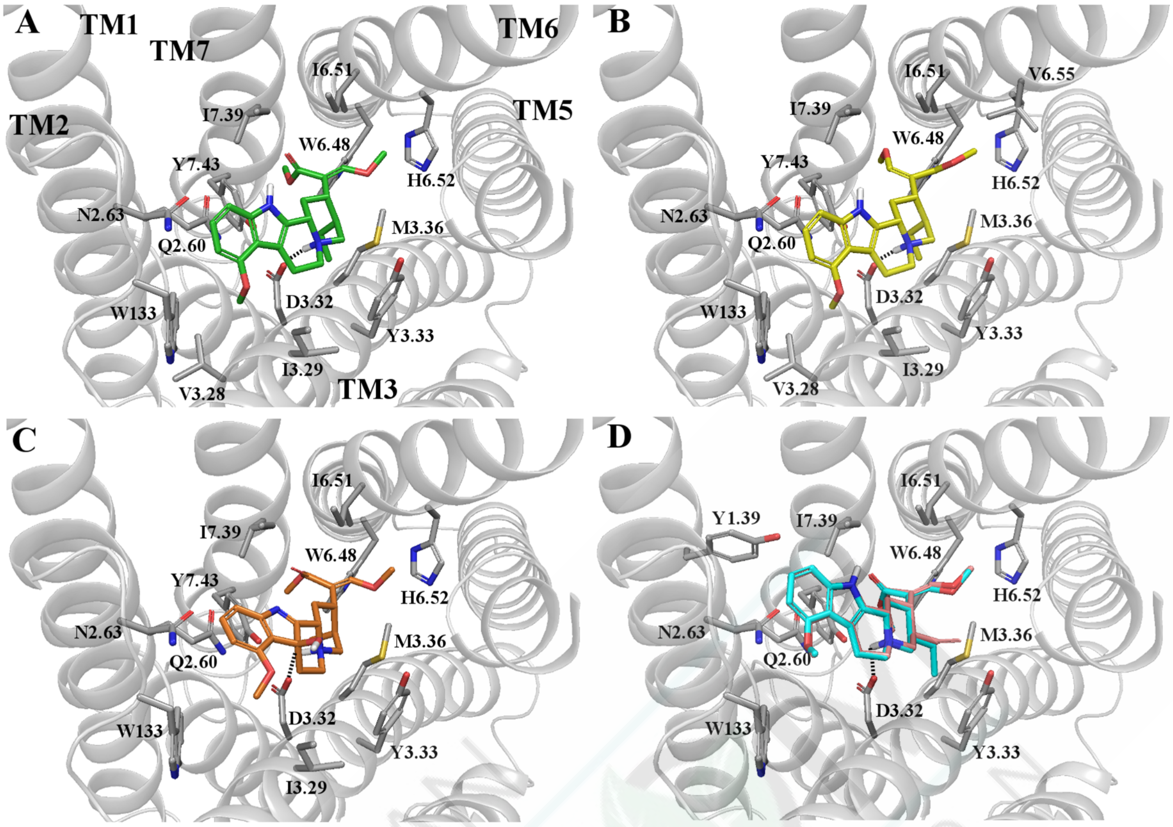


Figure 6. Docking of (−)-mitragynine and other analogues to the active μ-opioid receptor crystal structure. Top-scoring binding poses of (A) (−)-mitragynine, (B) (Z)-mitragynine, (C) 7-hydroxymitragynine, and (D) antagonists paynantheine (pink) and speciogynine (cyan). Only residue side chains within 4 Å of the ligand are reported. Polar interactions are shown as dotted lines. TM helices are shown in cartoon representation (in gray). ECL2 and part of TM5 have been omitted for clarity. Residues are labeled using one-letter amino acid code and Ballesteros and Weinstein's generic numbering scheme.

in reduced affinity for the active conformation of the receptor and corresponding antagonist activity. Consistent with the inverted stereochemistry of the core structure at position 3, docking of speciociliatine revealed a completely different binding pose with its indole group extending toward TM3 and forming a polar interaction with Y148$^{3.33}$ (Figure S8B and Table S3). Notably, unlike all other compounds reported here, the acrylate moiety in speciociliatine is in axial rather than equatorial position, pointing toward TM5 and TM6. All in all, a number of different stereochemical configurations in the *Mitragyna* alkaloid family appear to be sufficient to retain binding at hMOR, while the absolute stereochemistry found in mitragynine is required for activation of the receptor.

■ CONCLUSION

In this work, we have presented the first thorough, in vitro characterization of the opioid receptor pharmacology and signaling of the natural *Mitragyna* alkaloids in receptor-level functional assays. The partial agonist activity of (−)-mitragynine at MOR is likely to account for many of the effects of *Mitragyna speciosa* extracts in humans. However, the other major alkaloids isolated from the plant, paynanthiene, speciogynine, and speciociliatine, all exhibited competitive antagonist activity at this receptor. Considering that cumulatively, these secondary alkaloids accounted for an approximately equal percentage of the total alkaloid content compared to mitragynine in our extracts, the gross psychoactive effects of crude plant material are likely to represent a complex interplay of competing agonist and antagonist effects at the opioid receptors. It was also found that the potent oxidized analogue 7-OH is not necessarily present in all extracts of plant material (as previously suggested), so the potential contribution of this alkaloid to the effects of *Mitragyna speciosa* is not general, unless 7-OH is formed as a metabolite.

Exploration with several synthetic mitragynine analogues allowed us to define basic SAR at each of the existing substituents, including in regions (the D ring) that were only accessible to derivatization via total synthesis. This work revealed that opioid activity in the mitragynine scaffold is quite sensitive to structural modification and suggested that the *Mitragyna* alkaloids adopt a unique binding pose at MOR, distinct from that of classical opioids. This possibility was further supported by molecular docking studies at MOR. The first total synthesis of the unnatural enantiomer, (+)-mitragynine, likewise allowed us to confirm that the naturally occurring isomer is the more active opioid agonist.

We also found that mitragynine and 7-OH display biased signaling at MOR, being selective for the G protein pathway. Thus, it is hoped that this scaffold may represent a starting point for the development of novel opioid analgesics with reduced side effects. Relatedly, the finding that, in addition to their activity at MOR, both mitragynine and 7-OH are KOR antagonists, suggests that *Mitragyna* alkaloids or their synthetic derivatives may also serve as leads for novel dual-action antidepressants. In this regard, mitragynine itself is of particular interest, as it acts as both a low efficacy MOR partial agonist, and a KOR antagonist. Both of these mechanisms have been shown to elicit antidepressant effects in animals, and in the case of MOR, humans as well (see above). However, modulators of the KOR have received considerably more attention in the psychiatry community in recent years, likely due to their apparent lack of abuse potential. Antagonists of this receptor are antidepressant in animal models and oppose a variety of stress-related responses that are believed to be mediated through the endogenous KOR agonists, dynorphins.[61−63] Further, several agents in this class have entered clinical trials for MDD, but none have yet reached the market.[64] Given the ability of mitragynine to perturb both of these opioid signaling systems in the direction consistent with mood enhancement, it is unsurprising that it has been shown to exhibit antidepressant activity in the forced swim test (a rodent model of depression).[65] Therefore, *Mitragyna* alkaloids also hold promise in the treatment of mood disorders.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00360.

Copies of NMR spectra. (PDF)

Synthetic procedures and spectral data for all compounds, additional binding data at rodent receptors, additional functional data at rodent and human receptors, and additional docking results (PDF)

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Notes

The authors declare no competing financial interest.

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Total Synthesis of (-)-Mitragynine and Analogues

UNIVERSITEIT VAN AMSTERDAM

Master Thesis

by

Isabel Kerschgens

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Abstract

Mitragynine, paynantheine and speciogynine belong to the group of corynanthe alkaloids, a large class of biologically active indole alkaloids. Present in the leaves of the Asian plant *Mitragyna speciosa* (Rubiaceae) they have been used by Thai and Malaysian natives as a substitute for opium as well as for their stimulating activity. Besides the use as a drug, the plant has found application in medicine in the treatment of coughing, diarrhea, muscle pain and hypertension. Interestingly, mitragynine has a stronger analgesic effect than morphine, so that it has been suggested as a useful compound in the treatment of opiate addiction in replacement therapy. About the biological activity of paynantheine and speciogynine there are very little studies reported.

Three syntheses of mitragynine have been developed, two starting from enantiopure starting materials and a formal synthesis using organocatalysis. Syntheses of paynantheine and speciogynine have not been reported so far. Our approach to the three alkaloids proceeds via an asymmetric Pictet-Spengler reaction catalyzed by organic bifunctional cinchona alkaloids. This strategy allows fast and highly selective formation of the tetrahydro-*β*-carboline skeleton. The second key-step in the synthesis is a Tsuji-Trost allylic alkylation precedented in earlier work of our group. Based on achiral starting materials, a fast and enantioselective excess to mitragynine, paynantheine and speciogynine was established. Additionally, our method allows to design new unnatural derivatives which exhibit improved biological properties.

Table of Contents

1. Introduction 1

1.1. Mitragyna Speciosa 1

1.2. Structure of Mitragynine, Paynantheine and Speciogynine 3

1.3. Biological Activity of (-)-Mitragynine 3

1.4. Reported Syntheses of (-)-Mitragynine 4

1.4.1. *Synthesis by Takayama et al.* 5

1.4.2. *Synthesis by Cook et al.* 6

1.4.3. *Synthesis by Ma et al.* 9

1.5. Aim and Motivation of the Investigations 10

2. Synthesis of (-)-Mitragynine, (+)-Paynantheine and (+)-Speciogynine 11

2.1. Synthetic Strategy and Outline of This Thesis 11

2.2. Synthesis of the Components for the Pictet-Spengler Reaction 13

2.2.1. *Synthesis of the Tryptamine* 13

2.2.2. *Synthesis of the Aldehyde* 14

2.3. Asymmetric Pictet-Spengler Reaction 15

2.3.1. *Use of Binol-Phosphoric Acids as Organocatalysts* 17

2.3.2. *Use of Bifunctional Cinchona Alkaloids as Organocatalysts* 20

2.3.3. *Optimization of the Thiourea-Catalyzed Pictet-Spengler Reaction* 24

2.3.4. *Mechanistic Considerations Towards the Substrate-Catalyst Interaction* 26

2.3.5. *Necessity of Acid for the Pictet-Spengler Reaction* 29

2.4. Synthesis of the α-Keto-Ester 30

2.5. Tsuji-Trost Allylic Alkylation 32

2.6. Final Steps Towards (-)-Mitragynine 34

2.7. Final Steps Towards (+)-Paynantheine and (+)-Speciogynine 36

3. Conclusion 39
  3.1. Summary 39
  3.2. Comparison with Other Syntheses 40
  3.3. Conclusion 41
4. Abbreviations 43
5. Experimental 45
6. Acknowledgements 73
References 75

1. Introduction

1.1. Mitragyna Speciosa

Mitragyna speciosa is a tree growing in the tropical climate of Thailand and Malaysia whereas the leaves and extracts are commercially sold under the name ”Kratom”. The plant is classified as a representative of the family Rubiaceae which is also known as the “coffee family”. With only 10 species worldwide the genus of *Mitragyna* is relatively small.[1] Its popularity is based on its unique biological activity, so that the leaves have been traditionally consumed by natives of Thailand and Malaysia for over hundred years.

The extract of the plant has dose-dependent effects: a stimulating activity with small doses while higher amounts lead to euphoric and sedative effects.[1] Therefore, it has been applied as a substitute for opium by natives and has as well been considered as a helpful agent for replacement therapy in the western world. The leaves, either fresh or dried, and the resin were consumed mainly orally to release their relaxing or stimulating activity.[2, 3] Despite the use of *Mitragyna speciosa* as a drug, the plant has also found medicinal application in the treatment of coughing, diarrhea, muscle pain and hypertension.[4]

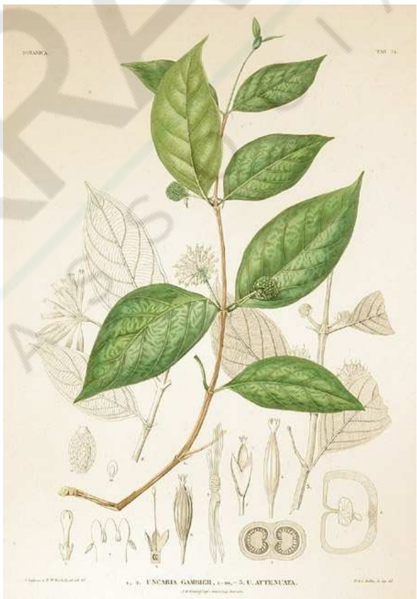
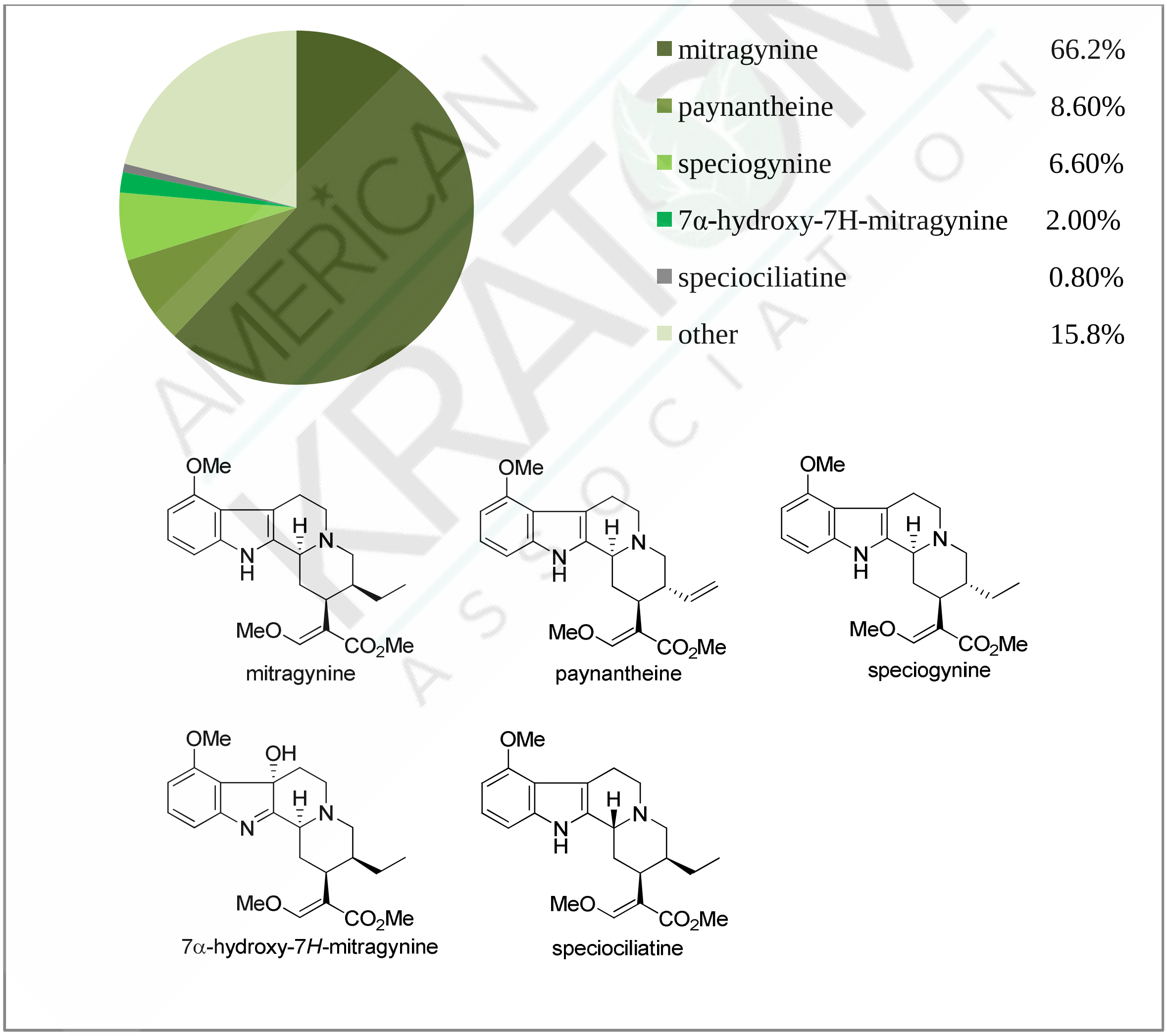

1, 2. UNCARIA GAMBIER, 3 - 10. - 5. U. ATTENUATA.

Figure 1: A picture of *Mitragyna speciosa* by the Dutch botanist Pieter Korthals[5]

Studies about chronic use of kratom revealed side effects like anorexia, weight loss, constipation and hyperpigmation of the face.[2, 3][6] Uncontrolled consumption of kratom can lead quickly to an addictive behavior with abstinence syndromes such as insomnia, lethargy, myalgia, arthralgia, aggression and myonclonus.[6] In Thailand it has therefore already been outlawed in 1939 through the “Kratom Act”. Later, countries such as Australia, Malaysia and Myanmar followed.[7] In the Western World however, the distribution over the internet proceeds rather uncontrolled.

Responsible for the biological activity of the tree are the compounds which are present in the leaves or the resin. These compounds (mainly alkaloids) are released during the consumption[a] to exhibit their desired effects. The alkaloid content of the leaves is about 0.5%[8] whereas the isolation of 44 different compounds has been reported over the last 87 years. The exact distribution of alkaloids varies depending on the region and each specific plant but mitragynine is generally obtained as the major constituent. In 2004 Takayama investigated the distribution of alkaloids with a plant growing on the campus of the Chulalongkorn University of Bangkok (Scheme 1).[9]



Scheme 1: Alkaloid distribution

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[a] Brewing the leaves in hot water and serving them as a tea, chewing the fresh leaves or smoking the resin.

More than half of the amount of isolated alkaloids turned out to be mitragynine with 66.2%, followed by paynantheine with 8.6% and speciogynine with 6.6%.

1.2. Structure of Mitragynine, Paynantheine and Speciogynine

The naturally occurring indole alkaloid (-)-mitragynine and its analogues (+)-paynantheine and (+)-speciogynine belong the class of corynanthe alkaloids. First isolated in 1965 by the group of Shellard[10] the final structure of mitragynine was confirmed by an X-ray analysis of the group of Zacharias with a mitragynine hydroiodide salt.[11] The isolation of paynantheine and speciogynine followed soon.[12, 13] Structurally, they all consist of an aromatic indole system bearing a methoxy-group at the 4-position. In addition to that, there are two six-membered rings both sharing nitrogen-4 and carbon-3. In total there are three stereocenters. Mitragynine and speciogynine only differ in the configuration of stereocenter C-20, so that both molecules are diastereomers of each other. Paynantheine and speciogynine have the same configuration at C-20 but paynantheine is bearing a vinyl-group at this position instead of an ethyl-group.

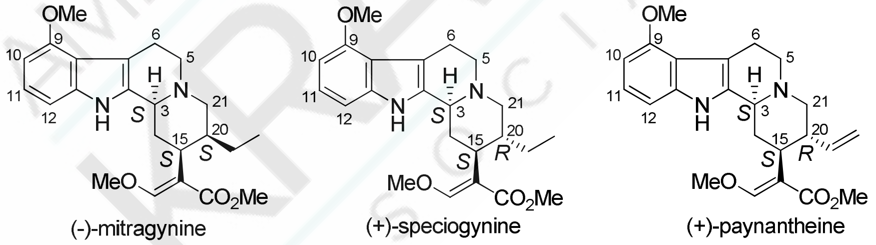
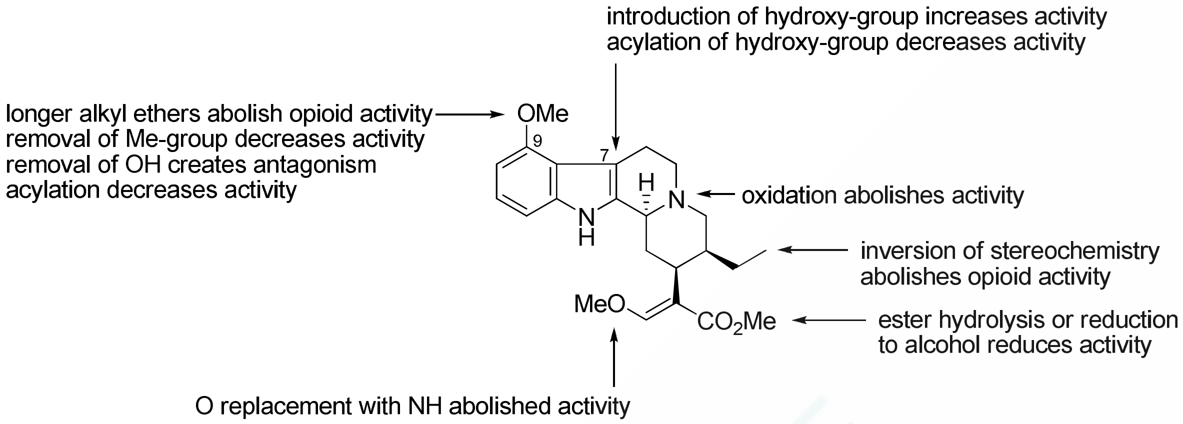


Figure 2: Structures of (-)-mitragynine, (+)-speciogynine and (+)-paynantheine

1.3. Biological Activity of (-)-Mitragynine

Although there are studies which deal with metabolism of paynantheine and speciogynine[14, 15] concrete studies on the biological activity are not reported so far. On the other hand, main alkaloid mitragynine has been investigated in more detail. In vivo and in vitro studies indicated that mitragynine is a central nervous system stimulant[3, 16] and primarily acts on μ-opioid receptors.[17, 18]

Studies about the relationship between structure of the molecule and biological activity are summarized in a review by McCurdy *et al.*[1] and are shown in Scheme 2.


introduction of hydroxy-group increases activity
acylation of hydroxy-group decreases activity
longer alkyl ethers abolish opioid activity
removal of Me-group decreases activity
removal of OH creates antagonism
acylation decreases activity
OMe
9
7
H
N
N
H
oxidation abolishes activity
inversion of stereochemistry
abolishes opioid activity
MeO
CO2Me
ester hydrolysis or reduction
to alcohol reduces activity
O replacement with NH abolished activity

Scheme 2: Structure and activity in (-)-mitragynine

First of all, the methoxy-group on the C-9 is essential for the biological activity. When the methoxy group is replaced by a longer alkoxy-group, the biological activity is abolished. When the group is removed completely to give the natural product corynantheidine an antagonist[b] is produced. This shows that modulation of this functionality can dramatically alter the biological properties of the molecule. Secondly, oxidation and introduction of a hydroxyl-group on the C-7 carbon with phenyliodine bis(trifluoroacetate)[19] give the 46-fold higher active 7α-hydroxy-7*H*-mitragynine (for the structure see Scheme 1).[8] Finally, loss of the basic character of the tertiary amine through oxidation as well as disruption of the *β*-methoxyacrylate moiety abolish the activity.[c]

1.4. Reported Syntheses of (-)-Mitragynine

Since the characterization of (-)-mitragynine through the crystal structure in 1965[11] there have been two syntheses of enantiopure mitragynine and one formal synthesis reported. The first one has been published in 1995 by Takayama *et al.* using chiral starting materials generated by enzymes.[20] Later, Cook *et al.* developed the second synhesis using a chiral auxiliary.[8] The first organocatalytic approach has been published very recently by Ma *et al*. with a formal synthesis of (-)-mitragynine.[21]

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[b] A receptor antagonist is drug that does not provoke a biological response itself upon binding to a receptor, but blocks or dampens agonist-mediated responses. Mitragynine on the contrary, belongs to the class of agonists.

[c] Unfortunately, the origin (references) of the semi-synthesis/SAR-studies are not mentioned in the review.

1.4.1. *Synthesis by Takayama et al.*

Takayama's synthesis starts with commercially available 6-chloronicotinic acid which is converted into the racemic acetate **2** and subjected to enzymatic hydrolysis to afford the resulting secondary alcohol **3** and acetate **4** in 100% *ee* (Scheme 3). In the next step the enantiopure alcohol was condensed with bromide **5**[d] in heated benzene and catalytic amount of sodium iodide to give pyridinium salt **6** in 56% yield. Reduction of the salt resulted in an allylic alcohol with two separable diastereomers **7** and **8**. Although two diastereomers have been formed it was assumed that through a Claisen-rearrangement and their corresponding chair-like transition states, the newly formed stereocenter can be controlled by the absolute configuration of C-19. Moreover, it was believed that the undesired configuration of stereocenter C-3 of diastereomer **8** could be converted into the desired one after the Claisen-rearrangement. Both diastereomers **7** and **8** were subjected to the Claisen-rearrangement with trimethyl orthoacetate and catalytic amounts of benzoic acid to give the corresponding acetates **11** and **12**. The configuration of C-3 in acetate **12** was inverted to **11** with an oxidation-reduction sequence via a 3,4-dehydroimmonium salt.

Next, a formyl-group was introduced in **11** at C-16 to give the resulting product **13** in 56% yield.[e] The formyl group was converted into the dimethyl acetal and then treated with KO*t*Bu to generate the corresponding enol ether **14** in the *trans* configuration. Stereoselective hydrogenation with PtO_2 gave (-)-mitragynine in 9 steps.

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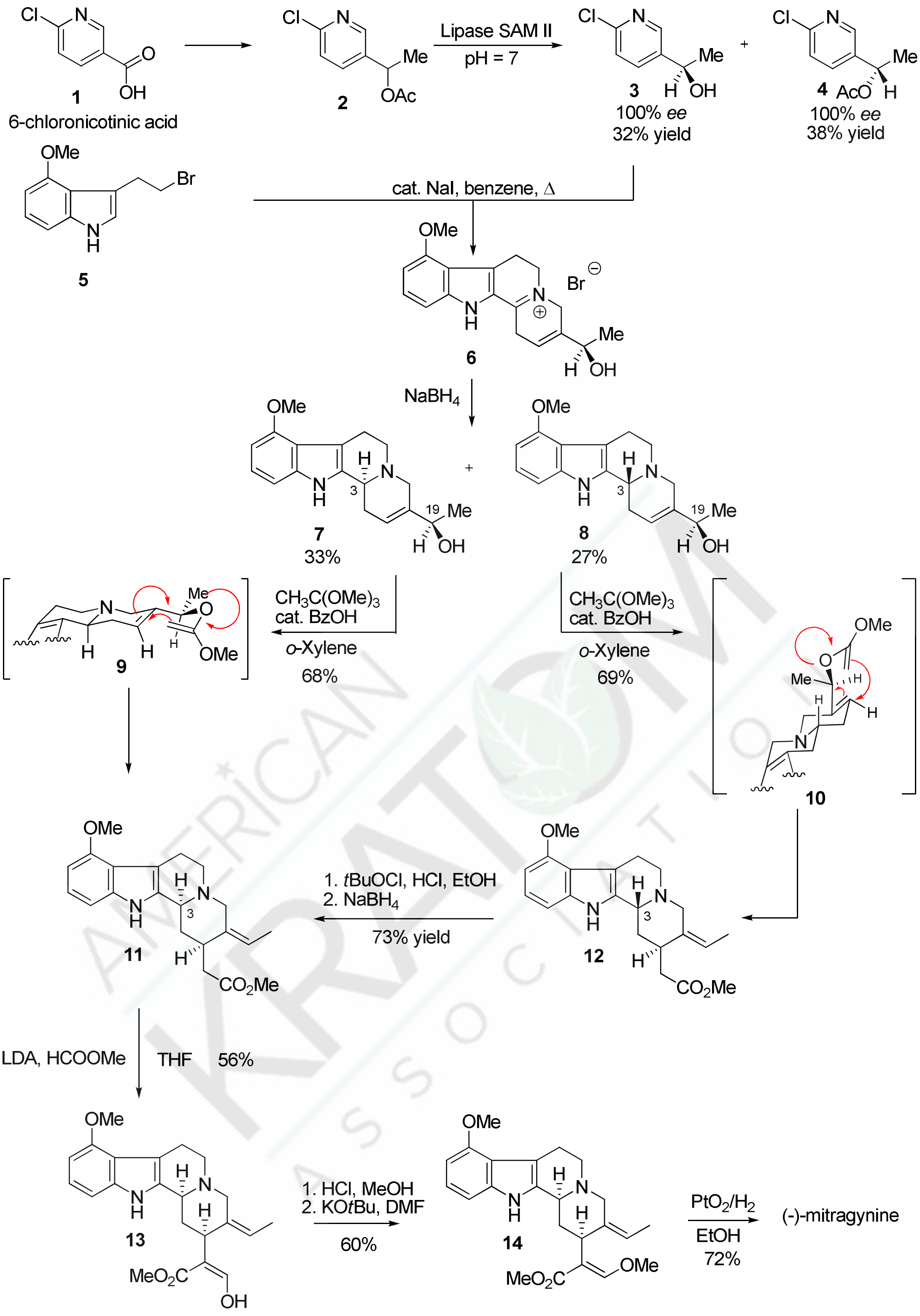
[d] 5-step synthesis, yields are not mentioned.

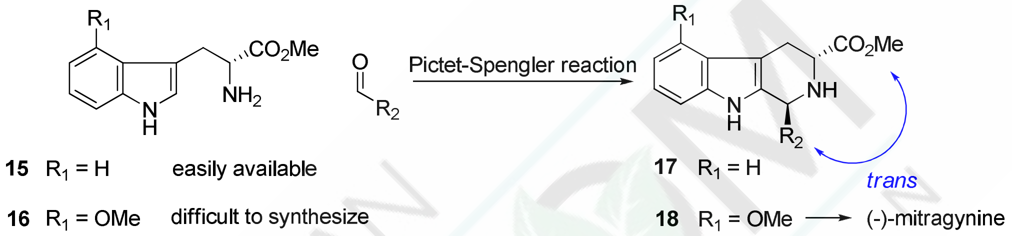
[e] The formyl group was obtained in the enol-form with the undesired *cis*-configuration.



Scheme 3: Total synthesis of (-)-mitragynine published by Takayama *et al*.

1.4.2. *Synthesis by Cook et al.*

James Cook from the University of Wisconsin-Milwaukee spent a lot of research on the chemistry of tryptophanesters. He found out that enantiopure tryptophan esters such as **15** undergo a Pictet-Spengler reaction with aldehydes to condensation product **17**[f] with the ester-group and the R_2-substituent *trans* to each other.[22, 23] With this *trans*-preference the stereochemistry of C-3 can be controlled in a diastereoselective fashion. Tryptophan esters are easily available from the naturally occurring amino acid tryptophan and the condensation product **17** resembles the core structure of mitragynine to great extend. Therefore, for the synthesis of mitragynine it would be the easiest to start from 4-methoxy-substituted tryptophan esters and to control the stereochemistry of the created stereocenter C-3 in condensation product **18** through the preferred *trans* relationship of the ester group and the R_2-substituent. Unfortunately, methoxy-substituted tryptophans are not available from nature. For the synthesis of (-)-mitragynine, as a consequence, first the methoxy-substituted tryptophan ester had to be synthesized.



Scheme 4: Tryptophan ester are desired compounds for the Pictet-Spengler reaction

To realize a synthesis of mitragynine, Cook *et al*. envisioned a chiral auxiliary approach for the preparation of enantiopure methoxy substituted tryptophan ester **18** using a modified Schöllkopf auxiliary (a bis-lactim derived from the amino acid valine). The synthesis starts with commercially available 3-methoxy-anilin which is easily converted into iodine **20**.[24] The iodine was coupled via a Larock heteroannulation[25] to a TMS propargyl-substituted Schöllkopf auxiliary.[26] At the same time the Boc-group on the indolic nitrogen was removed and the desired indole derivative **22** was obtained in 82% yield and >95% *ee*. Removal of the auxiliary went nicely in one step through hydrolysis with hydrochloric acid to give the desired methoxy-substituted tryptophanester **16**. Employing a sterically demanding substituent on the amine in three steps, the substrate **25** for the Pictet-Spengler reaction was obtained. With acetic acid and aldehyde **26** the Pictet-Spengler reaction was carried out in a diastereoselective fashion to the *trans* isomer **27**. From *trans*-tetrahydro-β-carboline **27** the two thiophenol groups were removed and a Ni(COD)$_2$ mediated cyclization was carried out with intermediate **28** to give **29**. From cyclized product **29** the ester-group was removed in three steps and the double bond of **30** selectively hydrogenated with Crabtree's catalyst. Five more steps from **31** gave (-)-mitragynine in >95% *ee* and an overall number of 22 steps.

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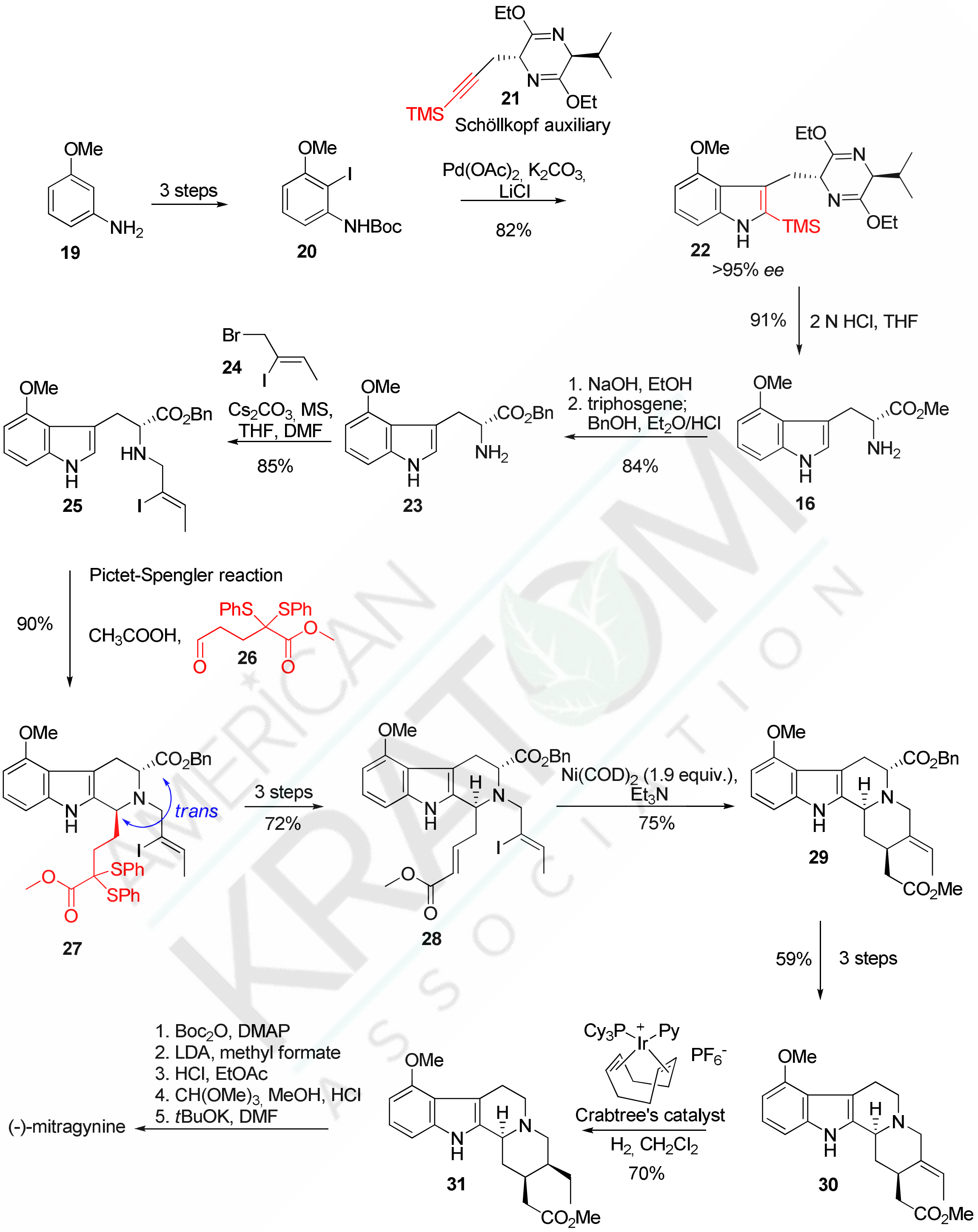
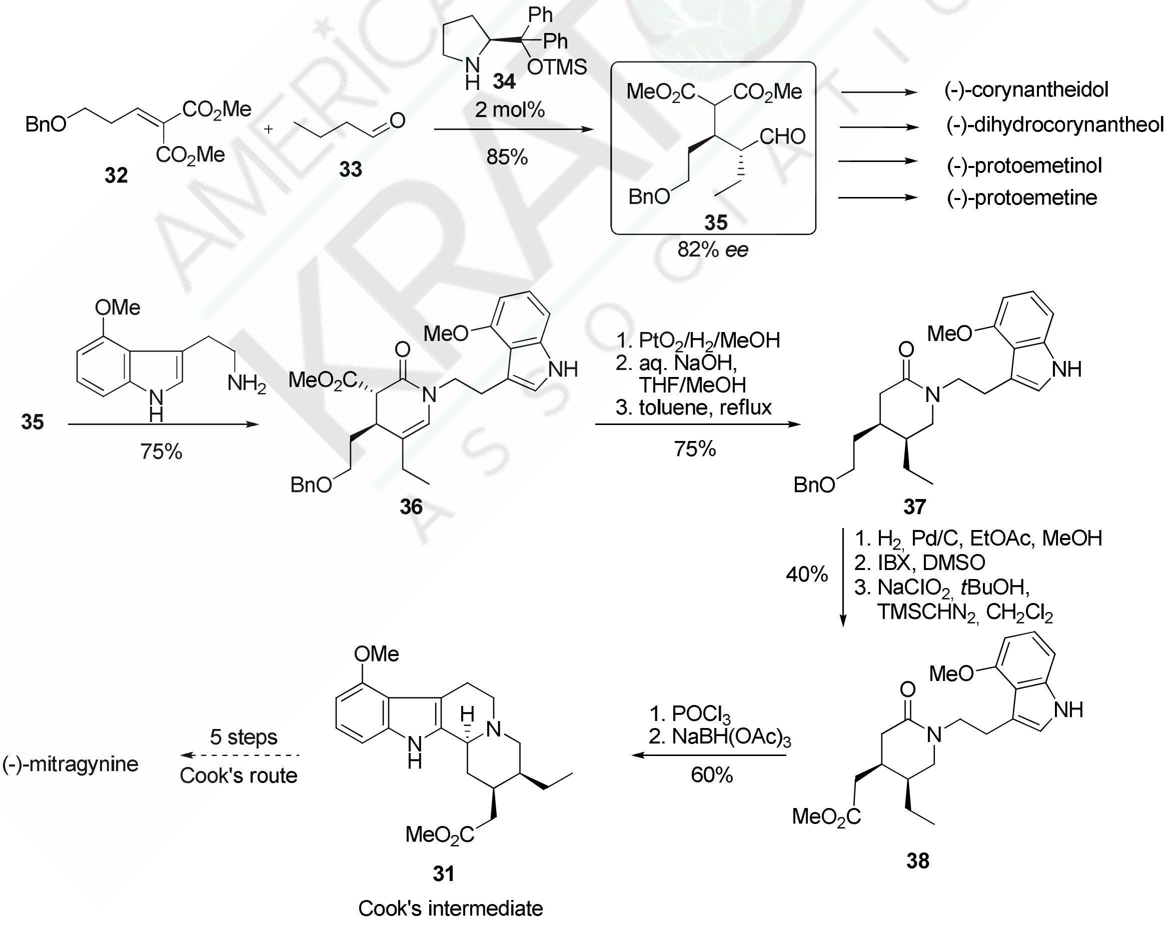
[f] This reaction will be later discussed extensively, but for now it is only important to know that a tryptamine reacts with an aldehyde to a system as **17**.



Scheme 5: Total synthesis of (-)-mitragynine by Cook *et al*.

1.4.3. *Synthesis by Ma et al.*

In 2011 Ma *et al*. published a formal synthesis of (-)-mitragynine using organocatalysis for the introduction of chirality.[21] The Key feature of their work is a chiral fragment synthesized via an organocatalyzed Michael-addition between **32** and *n*-butanal with *O*-TMS-protected diphenylprolinol **34**. **35** serves as a building block for the synthesis of several natural products as well as for (-)-mitragynine. The organocatalyzed Michael-addition went in good yield, unfortunately the *ee* dropped significantly when the reaction was performed on a 1 mmol scale (from 91% to 82% *ee*). Having fragment **35** at hand, this was coupled to 4-methoxy-substituted tryptamine via a reductive amination. **36** was then selectively hydrogenated and further subjected to saponification and decarboxylation to end up with lactam **37**. After debenzylation through Pd/C-catalyzed hydrogenation to give a primary alcohol, IBX-oxidation to the aldehyde, Pinnick oxidation to an acid and esterification, **37** was converted into **38**. Bischler-Napieralski cyclization followed by reduction afforded intermediate **31**, from which the synthesis could be finalized following Cook’s route (see Scheme 5).



Scheme 6: Formal synthesis of (-)-mitragynine published by Ma *et al*.

1.5. Aim and Motivation of the Investigations

Aim of this master project was to develop an efficient asymmetric synthesis of (-)-mitragynine, (+)-paynantheine and (+)-speciogynine.

Due to its unique biological activity (-)-mitragynine promises to be an interesting compound for medicinal applications. In contrast to mitragynine, there are hardly no studies known which deal with the medicinal evaluation of paynantheine and speciogynine. An easy access to these compounds through a chemical synthesis would facilitate the studies of these compounds. No synthesis for these compounds has been reported yet. Moreover, with a flexible synthetic strategy, not only the natural product itself but also derivatives with structural variation can be accessible. These compounds might have an increased or even different biological activity and are therefore interesting to investigate.

In addition to the accessibility of these compounds, chemists always aim for the development of new synthetic methods. Especially, the field of organocatalysis has grown exponentially over the last fifteen years. The use of small organic molecules functionalized as catalysts to perform a diversity of chemical reactions is strongly desired since they bring a number of advantages compared to metal- or biocatalysts.[g] Since the pioneer work in the early 2000s[27-34] many asymmetric organocatalytic methods have been developed. Based on these achievements it is a challenge to apply these methods in the total synthesis of complex natural products.

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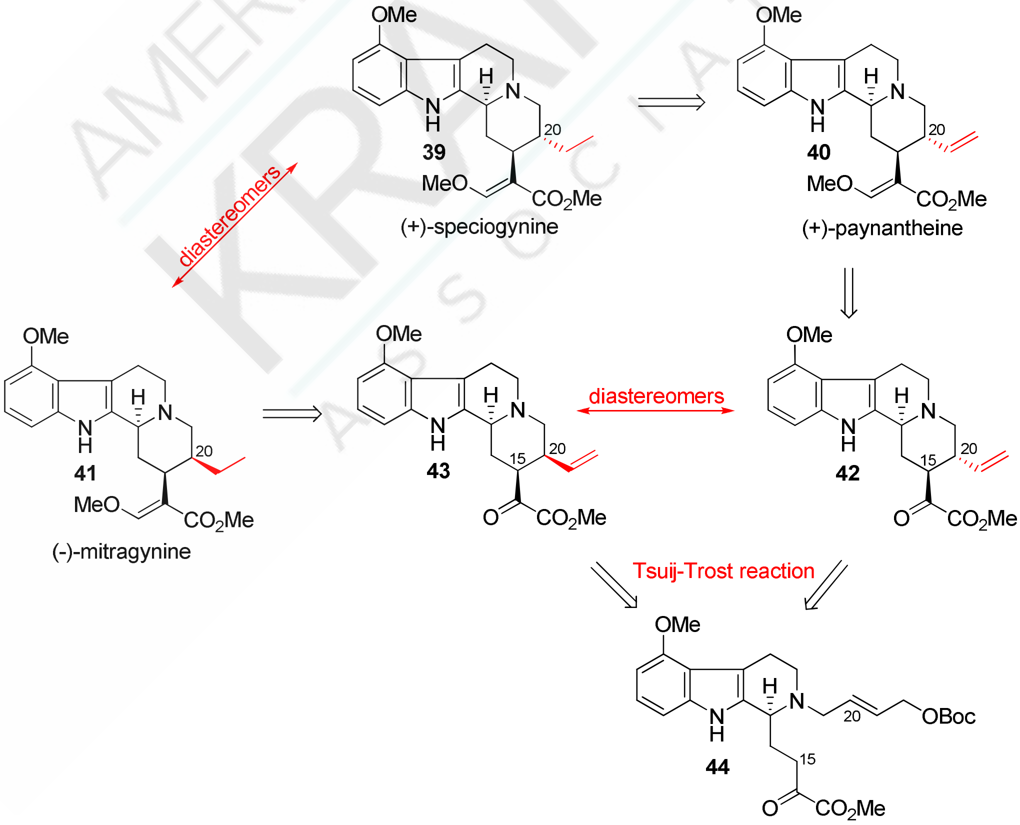
[g] Broad substrate scope, less toxic, easy handling.

2. Synthesis of (-)-Mitragynine, (+)-Paynantheine and (+)-Speciogynine

2.1. Synthetic Strategy and Outline of This Thesis

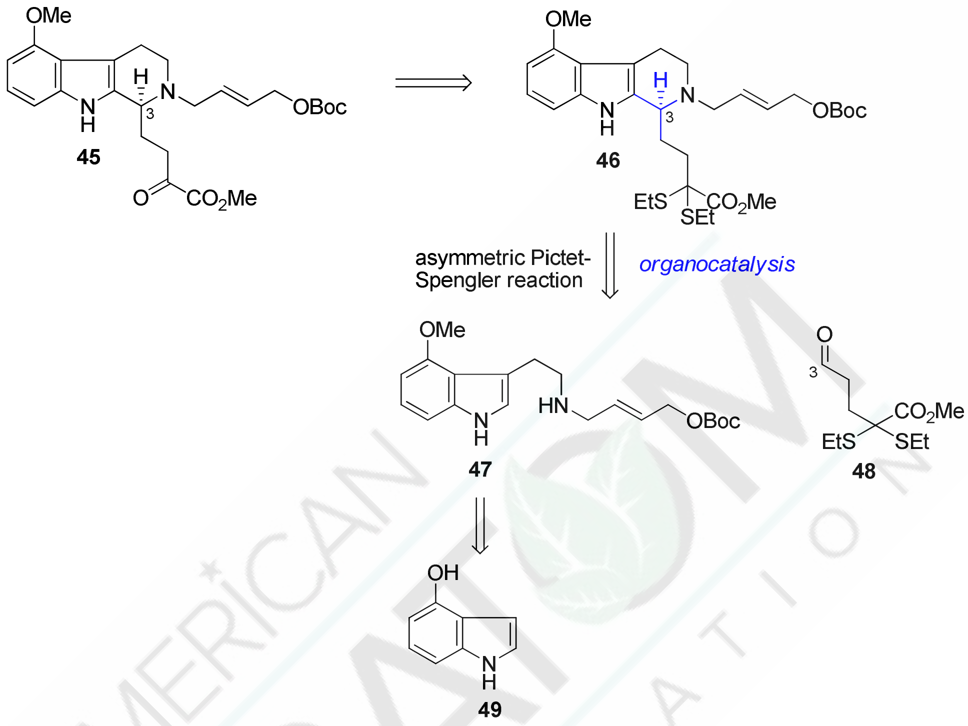
The retrosynthetic analysis of mitragynine, paynantheine and speciogynine is depicted in Scheme 7. Due to their strong structural resemblance it was envisioned that all three molecules can be generated through a common route which splits at a certain point later in the synthesis. This strategy has been applied before by our group in the synthesis of (-)-corynantheidine, (+)-corynantheine and (+)-dihydrocorynantheine.[35]

Starting the retrosynthesis, speciogynine **39** can be obtained from paynantheine **40** with hydrogenation of the vinylic substituent at C-20. Paynantheine **40** and mitragynine **41** both result from the corresponding α-keto-esters **43** and **42**. These two diastereomers are the products of a Tsuji-Trost reaction which functions as an intramolecular ring closing operation of intermediate **44**.



Scheme 7: Retrosynthesis I

α-Keto-ester **45** can be obtained from the corresponding thioacetal **46** which is the product of an asymmetric Pictet-Spengler reaction between tryptamine **47** and aldehyde **48** (Scheme 8). The Pictet-Spengler reaction should be carried out with a chiral organocatalyst. Tryptamine **47** was synthesized from commercially available 4-hydroxy-indole.



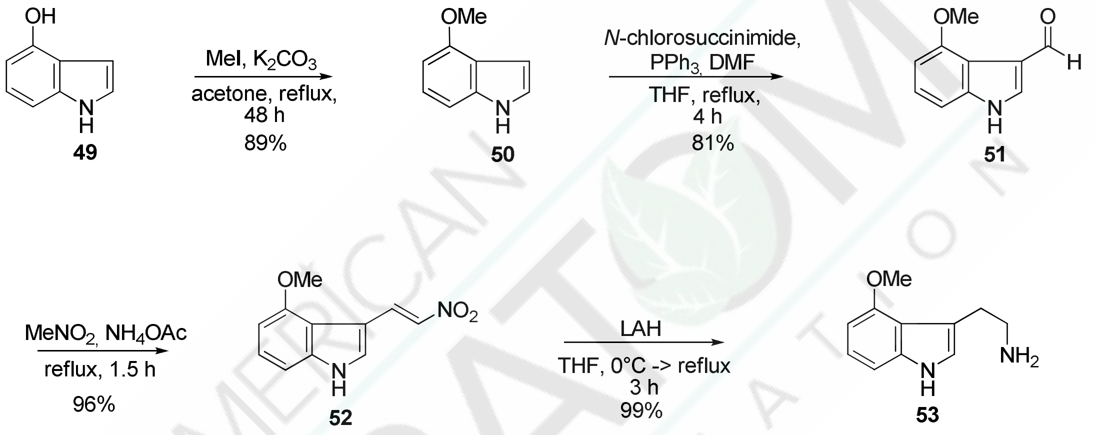
Scheme 8: Retrosynthesis II

The structure of this thesis is oriented along the retrosynthesis starting with the commercially available compounds and ending with the natural products mitragynine, paynantheine and speciogynine. First, the synthesis of tryptamine **35** starting from 4-hydroxy-indole and aldehyde **36** will be described. The next section deals with the key step of the synthesis, the asymmetric Pictet-Spengler reaction. Before the separation of the route in the two diastereomers via a Tsuji-Trost reaction, the transformation of the thioacetal into the ketone will be described. The last section deals with the finalization of the three syntheses.

2.2. Synthesis of the Components for the Pictet-Spengler Reaction

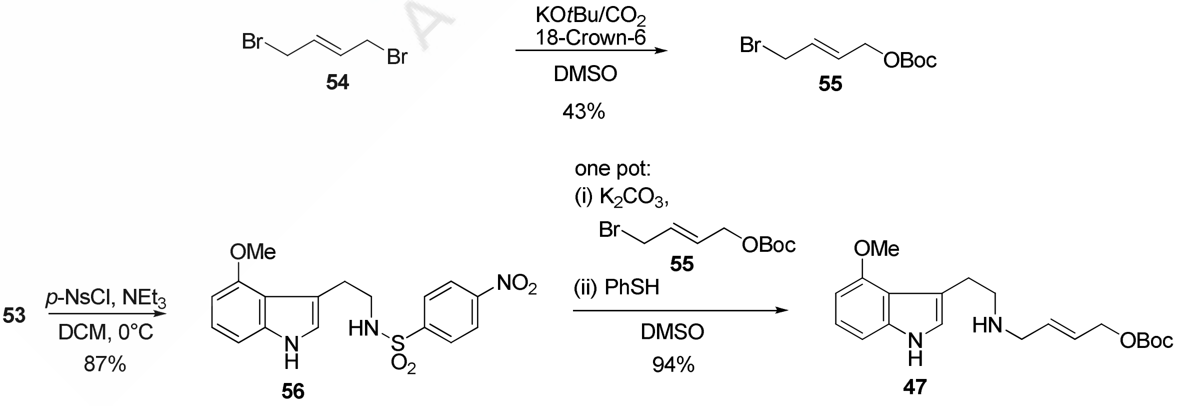
2.2.1. *Synthesis of the Tryptamine*

The synthesis of tryptamine **47** starts with commercially available 4-hydroxy-indole which was first methylated with iodomethane and potassium carbonate.[36] Next, 4-methoxy-indole **50** was formylated at the 3-position of the indole ring through a Vilsmeier-Haack reaction with *N*-chlorosuccinimide, triphenylphosphine and *N*,*N*-dimethylformamide to give aldehyde **51**.[37] Aldehyde **51** was treated with ammonium acetate and nitromethane to form first the Henry-product which immediately eliminates water to give the conjugated and therefore highly stable nitro alkene **52**. This was subsequently reduced to amine **53** with the help of lithium aluminum hydride.[38]



Scheme 9: Synthesis of the 4-methoxy-tryptamine

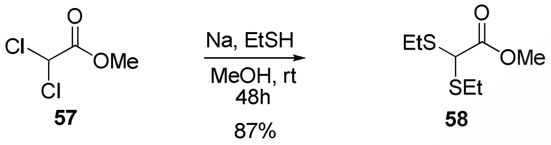
The synthesis of the functionalized amine **47**, was continued with protection of **53** using *p*-nosyl-chloride followed by alkylation with bromide **55** and deprotection after a Fukuyama protocol.[39, 40] The bromide **55** was synthesized in one step from (*E*)-1,4-dibromobut-2-en.[35]



Scheme 10: Synthesis of the functionalized tryptamine with help of a Fukayama protocol

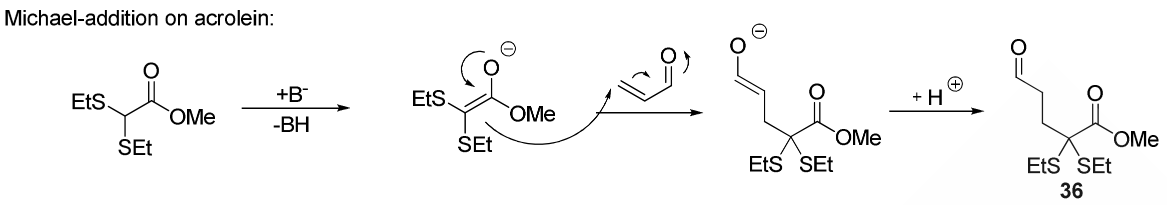
2.2.2. *Synthesis of the Aldehyde*

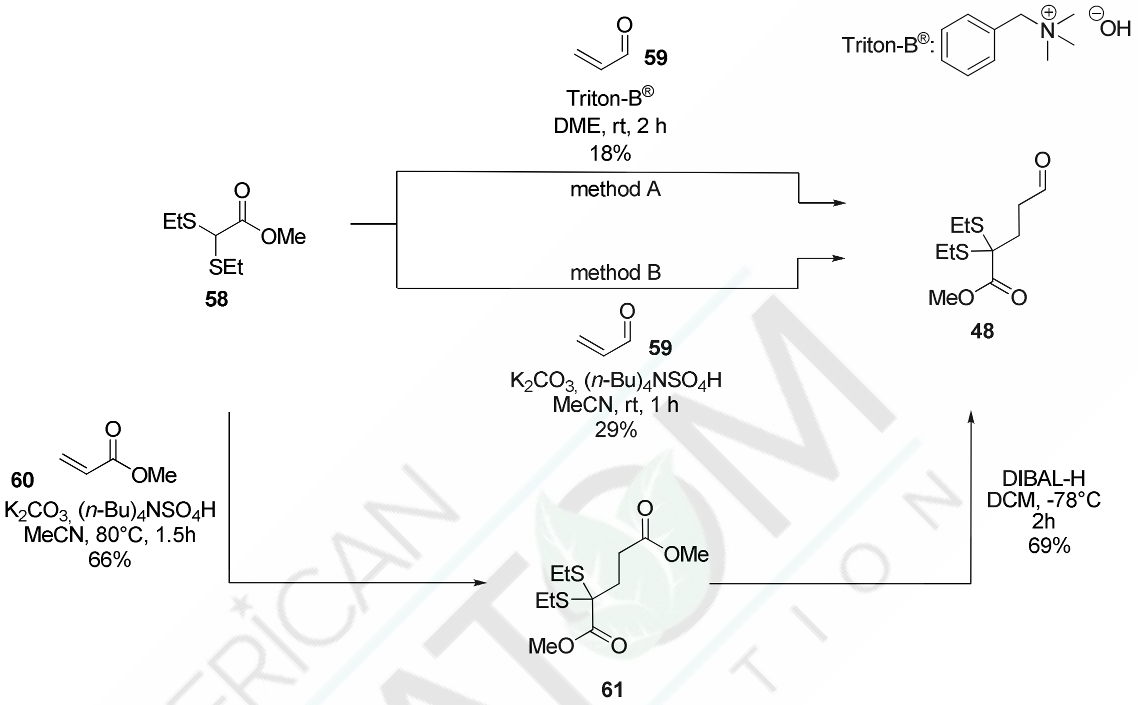
The synthesis of the aldehyde starts with installation of a thioacetal moiety in α-position to the ester group. This was realized with substitution of both chlorides of dichloroacetate **43** by ethanethiol (Scheme 11).[41]



Scheme 11: Synthesis of methyl bis(ethylthio)acetate

From **58** it was envisioned that after deprotonation a Michael-addition on acrolein would furnish aldehyde **48** (Scheme 12). As a first attempt Triton-B®, a quaternary ammonium hydroxide base, was applied with dimethoxyethane as a solvent for 2 h at room temperature (method A).[42] Unfortunately, the yield of 18% was rather disappointing. Therefore, another method was tried using tetrabutylammonium hydrogen sulfate in combination with potassium carbonate (method B).[43] The high reactivities of acrolein and the formed aldehyde both easily undergoing polymerization reactions are probably responsible for the low yield. In a third attempt to synthesize aldehyde **48** the same bases as for method B were applied in the Michael-addition this time on methyl acrylate instead on acrolein, followed by reduction of the resulting ester **61** with DIBAL-H. Although the overall yield for this method was higher than for method B, finally it was decided to synthesize the aldehyde with direct addition on acrolein due to the simplicity of the procedure and the fact that 20% starting material **58** was recoverable from the reaction.





Scheme 12: Different strategies for the synthesis of aldehyde **48**

2.3. Asymmetric Pictet-Spengler Reaction

The Pictet-Spengler reaction is an acid catalyzed ring closing reaction between a tryptamine and an aldehyde to form tetrahydro-β-carbolines.[a] Discovered in 1911 by Amé Pictet and Theodor Spengler[44] and extended to indole bases by Tatsui in 1928[45] the Pictet-Spengler reaction still remains one of the most important methods for the preparation of these tricyclic systems. The mechanism of the reaction starts with condensation of tryptamine **62** with an aldehyde to form first the corresponding hemi-aminal which looses water to form imine **65**. Protonation of the imine gives the iminium-ion intermediate **66** on which ring-closure occurs

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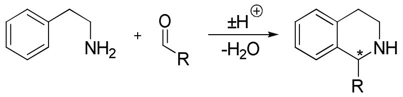
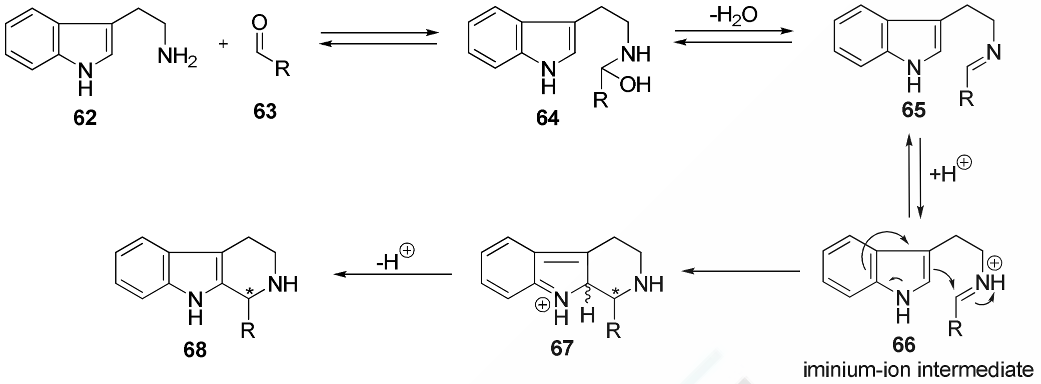
[a] The reaction can also be applied to phenylethylamines to form tetrahydroisoquinolines.

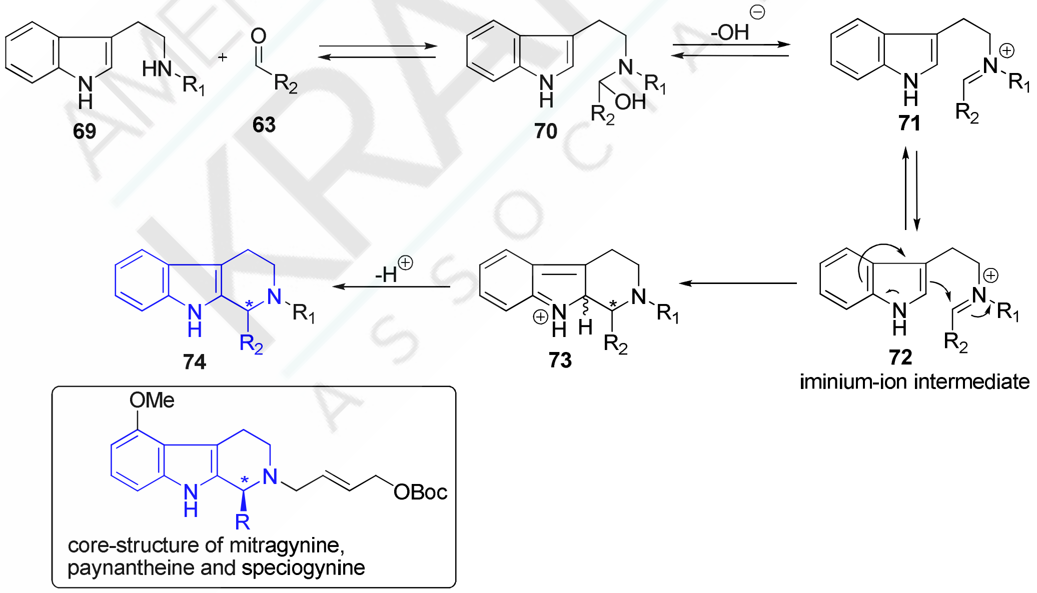


initiated by the electron rich indole system in a Mannich-type fashion. This step is not only enantiodiscriminating but has as well been reported as the rate-determining step.[46] With loss of a proton, **67** re-aromatizes to the tetrahydro-*β*-carboline **68**.



Scheme 13: Mechanism of the Pictet-Spengler reaction with unsubstituted tryptamines

For substituted tryptamines the mechanism is slightly different. Because of the substituent on the N_b-nitrogen the iminium-ion formation does not occur via protonation, but through loss of the hydroxyl-group of the hemi-aminal. Therefore, acid is not necessarily required for this process.

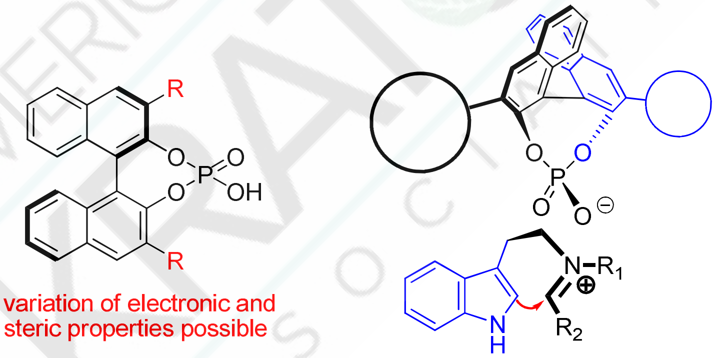


Scheme 14: Mechanism of the Pictet-Spengler reaction with substituted tryptamines

Since the tetrahydro-*β*-carboline core structure is present in many natural products, the Pictet-Spengler reaction became a useful tool for the preparation of these systems.[47, 48] After two decades of research using auxiliaries and chiral starting materials to create enantiopure tetrahydro-*β*-carbolines the first catalytic and at the same time organocatalyzed approach was published in 2004.[49] The group of Jacobsen used a thiourea as an organocatalyst for the enantioselective synthesis of these compounds. Other publications utilizing organocatalysts with high enantioselectivity in the Pictet-Spengler reaction followed.[50-52] Because of the applicability and usefulness of the method, it was envisioned to use organocatalysis in the synthesis of (-)-mitragynine, (+)-paynantheine and (+)-speciogynine as well.

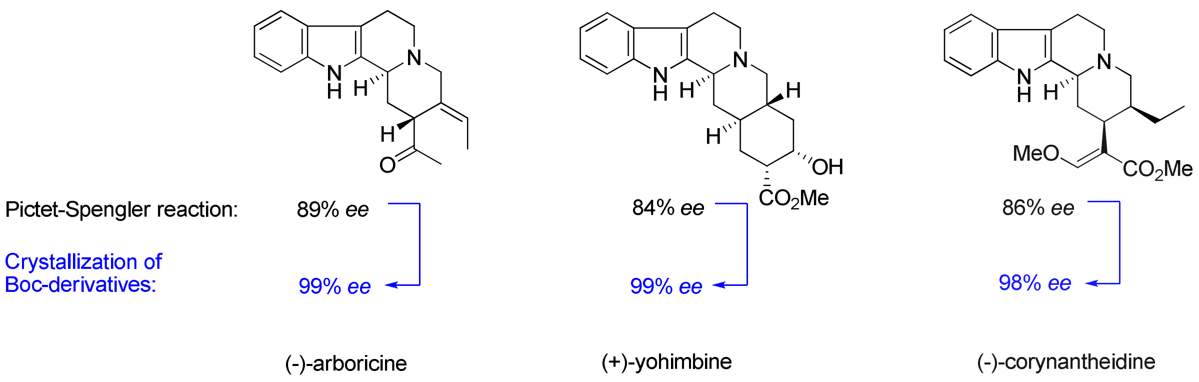
2.3.1. *Use of Binol-Phosphoric Acids as Organocatalysts*

First applied by List in 2006, BINOL-phosphoric acids evolved to widely applicable catalysts for the Pictet-Spengler reaction.[50] The versatile variation of the chiral backbone allows steric and electronic tuning depending on the required properties for the reaction. The interaction of the catalyst with the substrate is depicted in Scheme 15. BINOL phosphoric acids are suitable catalysts for the reaction because the anionic form of the acid is able to coordinate to the iminium ion intermediate via ion attraction. The backbone of the catalyst creates a chiral environment around the substrate in which ring-closure occurs selectively from one side. The interaction of the organocatalyst with the substrate and the resulting stereochemistry are therefore established in the rate-determining step.



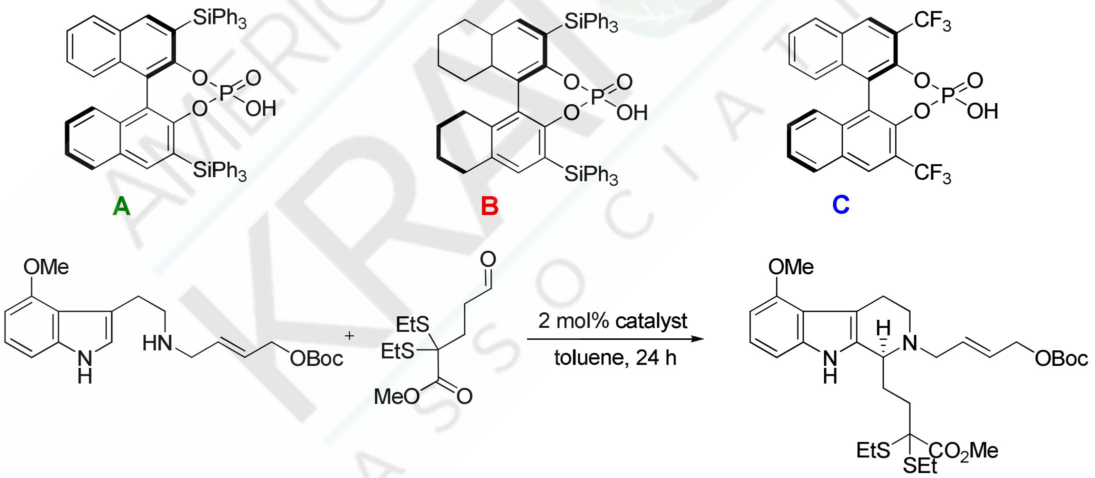
Scheme 15: Interaction of BINOL-phosphoric anion with the iminium-ion intermediate

In our group, BINOL-phosphoric acids have been applied in the synthesis of several natural products (Scheme 16).[53-55] In the synthesis of arboricine, yohimbine as well as corynantheine, the Pictet-Spengler reaction was carried out with very good enantioselectivity. Later in the syntheses, when a Boc-group was installed on the indolic nitrogen, the intermediates were crystallized to higher *ee* to furnish the end-products in high enantiomeric purity.



Scheme 16: Natural products synthesized through an asymmetric Pictet-Spengler reaction

To determine the applicability of BINOL-phosphoric acids in the synthesis of mitragynine, paynantheine and speciogynine three different catalysts (Scheme 17) were screened in the Pictet-Spengler reaction. Catalyst A and B are sterically different since the backbone of catalyst B is hydrogenated, whereas catalyst C differs in the electronegativity of the substituent at the 3-position.



Scheme 17: Pictet-Spengler reaction with BINOL-phosphoric acids

1. Variation of the Catalyst

The reactions were performed with 2 mol% catalyst, 1.2 equivalents of aldehyde and molecular sieves as a drying agent at room temperature for 24 h. The results of the reactions are shown in the table below. Unfortunately, the catalysts seemed to be completely unsuccessful in introducing chirality to the reaction. The measured *ee*s were very low and although all catalysts had the same chirality, different enantiomers were obtained.

entry	catalyst	drying agent	temperature	*ee* [%]
1	A	MS 4 Å	0 °C	-3
2	B	MS 4 Å	0 °C	7
3	C	MS 4 Å	0 °C	7

Table 1: Variation of the catalyst

2. Variation of the Temperature

Next it was tried to improve the results of the previous experiments by variation of the temperature (Table 2). Again low *ee*s were obtained and the enantiomeric outcome seemed random.

entry	catalyst	drying agent	temperature	*ee* [%]
1	A	MS 4 Å	-10 °C	-2
2	B	MS 4 Å	-10 °C	-6
3	C	MS 4 Å	-10 °C	0
4	A	MS 4 Å	-78 °C	11

Table 2: Variation of the temperature

3. Variation of Drying Agents

During the investigations on the phosphoric acid catalyzed Pictet-Spengler reaction it was noticed that the reaction already proceeds when no chiral acid was used. It was discovered that the molecular sieves were responsible for the fast product formation and obviously had sufficient catalytic activity for our system. Originally, the molecular sieves were intended to work as a drying agent to keep away the water which might interfere in the interaction of the catalyst with the substrate. As a consequence, it was concluded that when no drying agent or other drying agents were used, the BINOL-phosphoric acids were able to catalyze the process. Other drying agents such as $MgSO_4$ and Na_2SO_4 (entries 1 and 2 in Table 3) were expected to lack any catalytic activity. Unfortunately, for $MgSO_4$ hardly no product was formed and for Na_2SO_4 the *ee* was really low. When no drying agent was applied and the reaction was performed with BINOL-phosphoric acids only the *ee* was unsatisfactory as well.[b] At this stage no further attempts were made using phosphoric acids in this reaction.

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[b] Even when the catalyst loading was increased by twice the amount, no change in the *ee* was observed.

entry	catalyst	drying agent	temperature	*ee* [%]
1	B	MgSO4	-10 °C	-
2	B	Na_2SO4	-10 °C	-9
3	B	-	0°C	-10

Table 3: Variation of drying agents

2.3.2. *Use of Bifunctional Cinchona Alkaloids as Organocatalysts*

Inspired by the work of Jacobsen who used thiourea catalysts in his Pictet-Spengler reactions,[49, 56, 57] the bifunctional catalyst developed by Takemoto[58] was applied to the reaction. The catalyst contains a thiourea functionality which is able to increase the electrophilicity of carbonyl groups through coordination. Additionally, a tertiary amine is able to abstract hydrogens and thus donate electrons due to its Lewis-basic character.

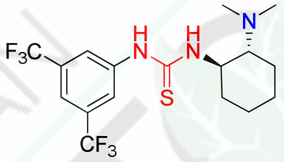
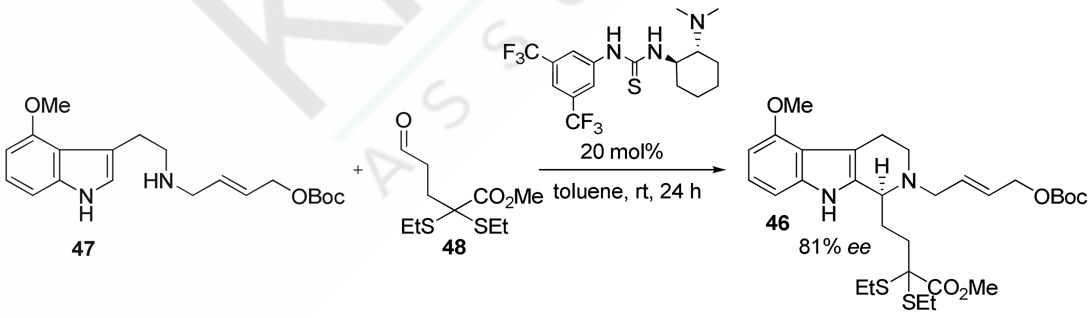


Figure 3: Takemoto catalyst

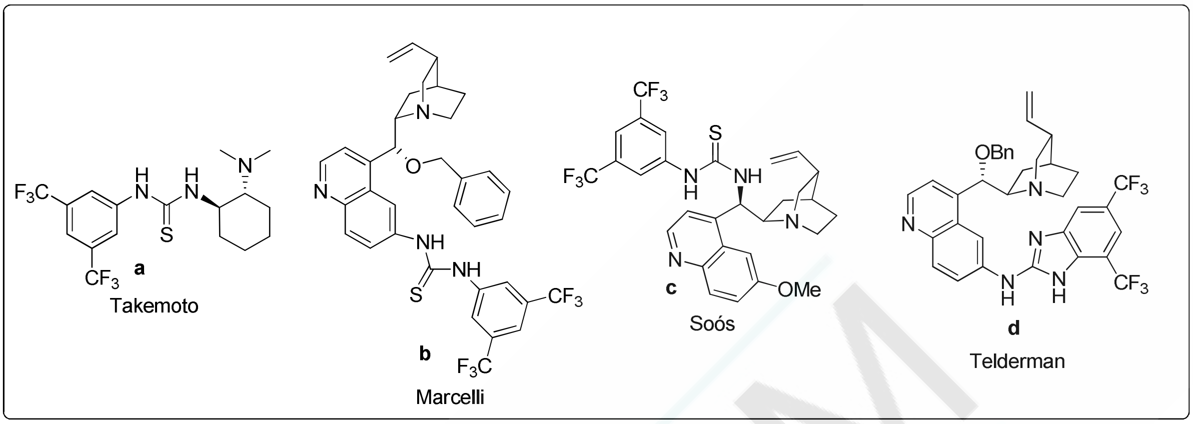
The catalyst was applied in 20 mol%, a normal catalyst loading for thiourea catalysts. Fortunately, the catalyst was extraordinarily good and gave an *ee* of 81% (Scheme 18).



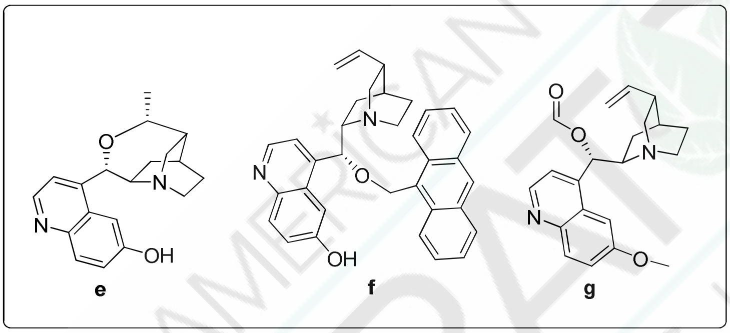
Scheme 18: Takemoto's catalyst in the Pictet-Spengler reaction

This result encouraged us to investigate the bifunctional catalyzed Pictet-Spengler reaction in more detail (Table 4). When the catalyst loading of Takemoto's catalyst was reduced to 10 mol%, the *ee* dropped by 20% (entry 1). Other catalysts such as **b**,[59] carrying the thiourea at the quinoline part, or **d**,[60] bearing a benzimidazole at this position, were not successful and gave a very low enantioselectivity as well as an unclean reaction. Catalyst **c** developed by the Soós group gave by far the best result.[61] The observed *ee* of 89% was even higher than the *ee* obtained with the Takemoto catalyst. To find out whether the basic nitrogen or the thiourea group was responsible for the catalysis, catalysts **e-g**[62, 63] and one of Jacobsen's commercially available thiourea catalysts **h** were applied.[57, 64]

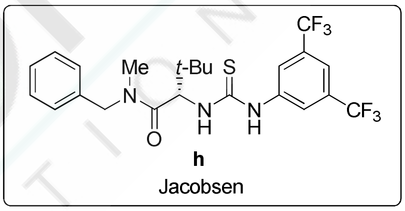
bifunctional catalysts



cinchona catalysts



thiourea catalyst

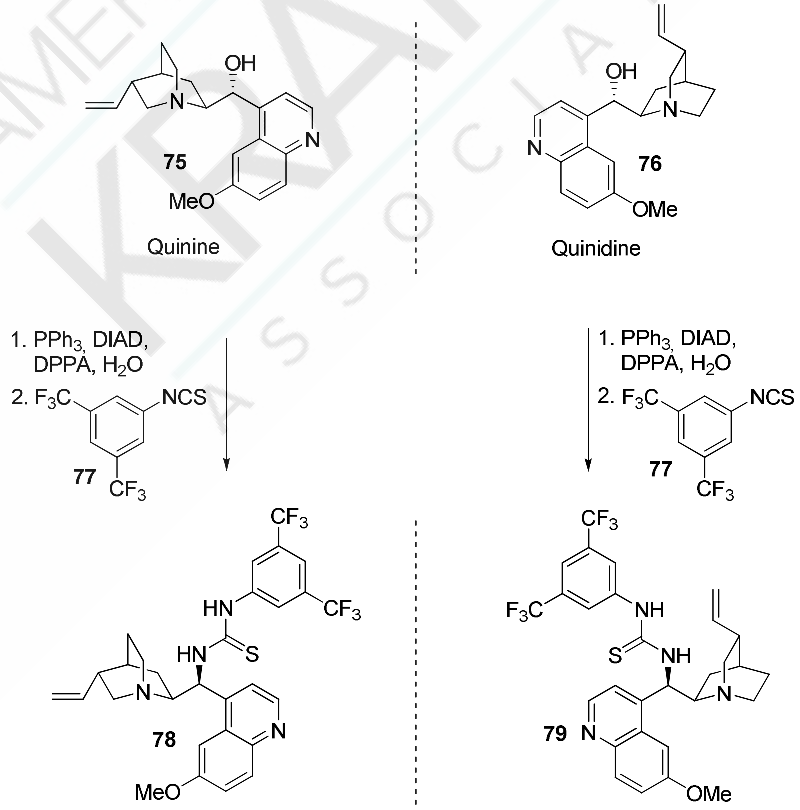


entry	catalyst	cat. loading	solvent	time	temperature	yield[a]	ee [%]
1	a	0.1	toluene	3 d	rt	47	-60
2	a	0.2	toluene	4 d	rt	57	-81
3	b	0.2	toluene	3 d	rt	29	-7
4	c	0.2	toluene	3 d	rt	90	-89
5	d	0.2	toluene	2 d	rt	71	-5
6[b]	e	0.2	toluene	5 d	rt→ 70°C	57	-11
7[c]	f	0.2	toluene/DCM	2 d	rt	58	-2
8[b]	g	0.2	toluene	5 d	rt→ 70°C	63	-6
9	h	0.2	toluene	2 d	rt	68	53
10[d]	h	0.2	toluene	2 d	rt	99	10

[a] determined by weight, [b] after 4 days very little conversion was obtained, the solution was heated to 70°C for 4 h; [c] due to the insolubility of the catalyst in pure toluene 50% DCM were added; [d] BzOH was used as an additive (20 mol%).

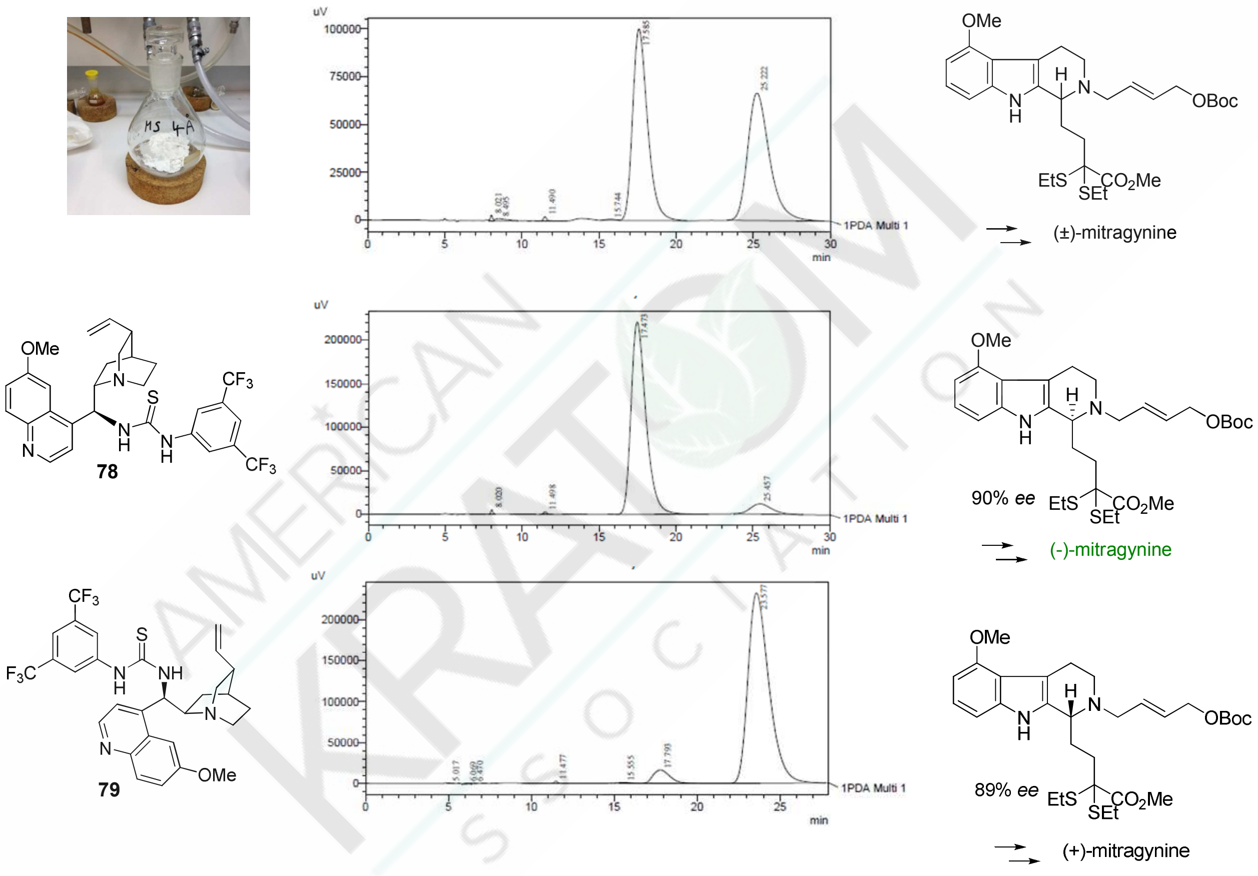
Table 4: Catalyst screening

Basic catalysts **e** and **g** gave low *ee*s and the reactions were slow so that heating was required to get some product formation. In these cases product formation occurs just by addition of enough activation energy but not necessarily catalyzed by the bifunctional catalyst. Catalyst **f** showed a really unclean reaction and low *ee* as well. The Jacobsen catalyst gave an enantiomerically enriched product of 53% *ee* but an unclean mixture was observed (entry 9). When benzoic acid is added as a co-catalyst the *ee* dropped to 10% (entry 10). Obviously, the best results were obtained using bifunctional catalysts like **a** and **c** which carry a thiourea group and a basic tertiary amine. The good stereoinduction and the similar results of both catalysts probably result from the close proximity of the thiourea group to the quinuclidine system. The functional groups are close together and the system allows less flexibility than catalyst **b** or **d**. Catalyst **c** can be synthesized from the natural product quinidine **76**, an alkaloid isolated from the Chinchona bark, a number of small trees native to South America.[65] The pseudoenantiomer of quinidine, quinine **75** is also isolated from the same tree species and only the position of the vinyl group keeps them apart from being exact enantiomers. From both pseudoenantiomers catalysts **78** and **79** can be obtained by a Mitsunobu-Staudinger sequence were the alcohol is converted into an amine followed by addition of the amine to an isothiocyanate to introduce the thiourea functionality.[61] This process is easily scalable, so that several grams of the catalyst were accessible.



Scheme 19: Synthesis of the Soós catalyst

With both pseudoenantiomeric forms of the catalyst at hand we were then able to synthesize both enantiomers in the Pictet-Spengler reaction. From the reaction with molecular sieves 4 Å we had access to the racemic product.[c] In Scheme 20 the chromatograms of the chiral HPLC measurements are depicted. Using catalyst **78** derived from quinine the intermediate leading to natural (-)-mitragynine becomes accessible. With the other catalyst **79**, the route towards (+)-mitragynine can be established, offering the possibility to investigate the difference in biological activity between the two enantiomers.



Scheme 20: Enantiomers available from the Pictet-Spengler reaction

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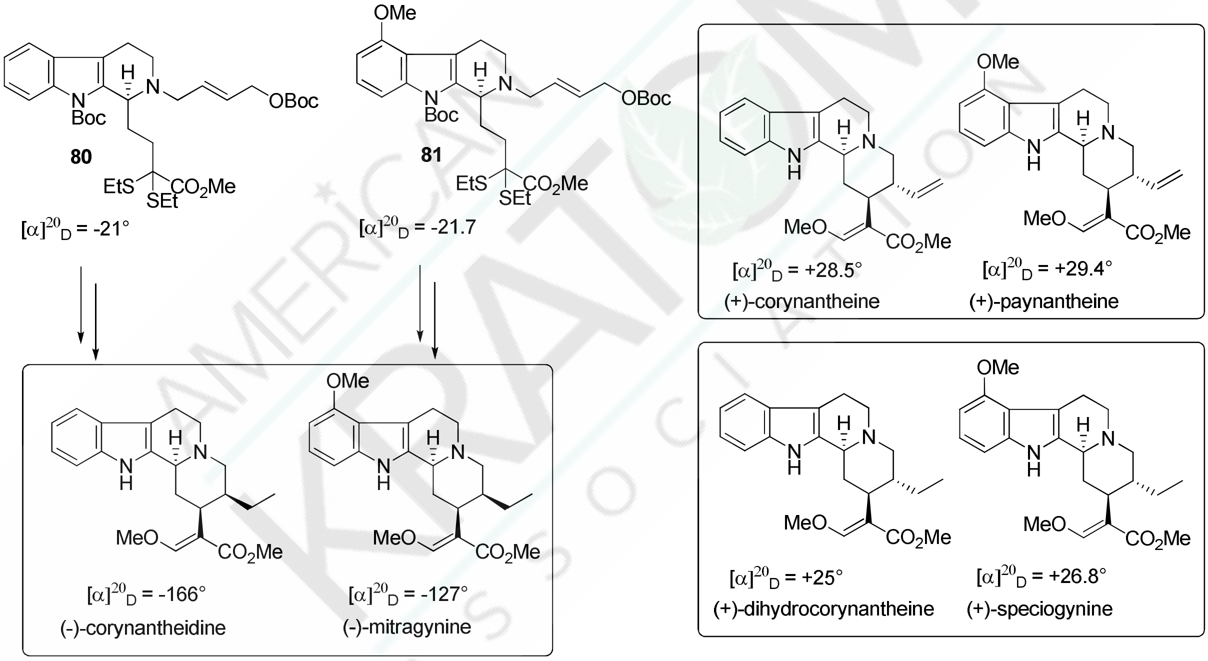
[c] The molecular sieves also functioned nicely as a catalyst up to a 6 mmol scale.

2.3.3. *Optimization of the Thiourea-Catalyzed Pictet-Spengler Reaction*

Having obtained good results with the Soós catalyst it was tried to further enhance the *ee* through variation of the conditions. It was measured that with catalyst **79** the order of elution in the chiral HPLC was the same as for the corynanthe alkaloids.[d] Because of that it was assumed that with catalyst **79**, the right enantiomer is obtained. When the optical rotation was determined later, it turned out that an opposite direction was observed than for the intermediate of the (-)-corynantheidine-synthesis.[55] There is a close analogy of optical rotations between the natural products mitragynine and corynantheidine, paynantheine and corynantheine as well as for speciogynine and dihydrocorynantheine (Scheme 21). Therefore, it can be concluded that both Pictet-Spengler products **80** and **81** should have the same optical rotation. Hence, the enantiomers of mitragynine and corynantheidine elute in reversed order in HPLC. To synthesize the enantiomer **81** which leads to (-)-mitragynine catalyst **78** is required instead of **79**. This was found, after the optimization experiments were carried out.



Scheme 21: Resemblance of optical rotation and structure

The optimization experiments were performed with catalyst **79** as shown in Table 5. All reactions were carried out over 24 h and the *ee* was determined by chiral HPLC. Important to mention: in all experiments the same batches of tryptamine, aldehyde and catalyst were used to exclude a deviation of the results depending on the starting materials. Entry 1 of

Table 5 shows the initial experiment carried out in toluene at room temperature for 24 h where an *ee* of 89% was observed. Firstly, the temperature of the reaction was changed

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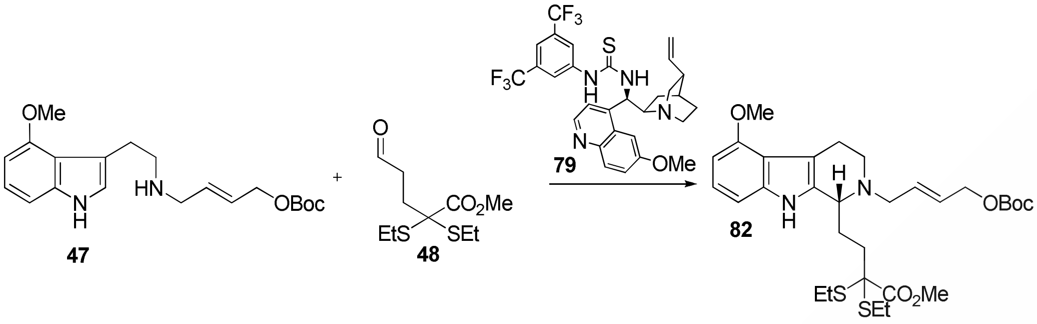
[d] Very similar natural product series, recently synthesized by our group.

(entries 2-4). Surprisingly the *ee* decreased with lower temperatures. When the temperature was increased a slightly lower *ee* was observed which shows that room temperature seems to be the optimal temperature for the reaction. Variation of the solvent (entries 5-8) did not result in an increase of the *ee*. Ethers such as THF and *n*-dibutylether gave the lowest enantioselectivity probably due to disturbance of the catalyst-substrate interaction through the lone-pair bearing oxygens. The addition of drying agents to absorb water which is released from the reaction (entries 9-11) did not result in significant improvement of the enantiomeric excess. Usually, water strongly disturbs the catalysis as was often observed for BINOL-phosphoric acids.[51] In our case, water seems not to have a strong influence on the *ee*. Finally, optimization of the catalyst loading was studied. Although the catalyst is easy to make it would be advantageous to reduce the catalyst loading to less than 20 mol%. With a lower amount of catalyst, the enantioselectivity decreased significantly (entries 12 and 13). Using a higher catalyst loading (entry 14), however, did not improve the *ee* in comparison to the initial experiment with 20 mol%. In addition to the experiments shown in the table, the dependence of the *ee* on the equivalent of aldehyde and the molarity of the reaction were investigated. It was observed, that the amount of aldehyde did not have any influence on the selectivity of the reaction, so did the concentration. Previous reports stated that there is a strong dependence of the enantiomeric excess on the concentration caused by possible complexation of the catalyst.[66] Using solutions of different molarity, however, did not verify this result. Overall, the reaction showed strong reproducibility and robustness.

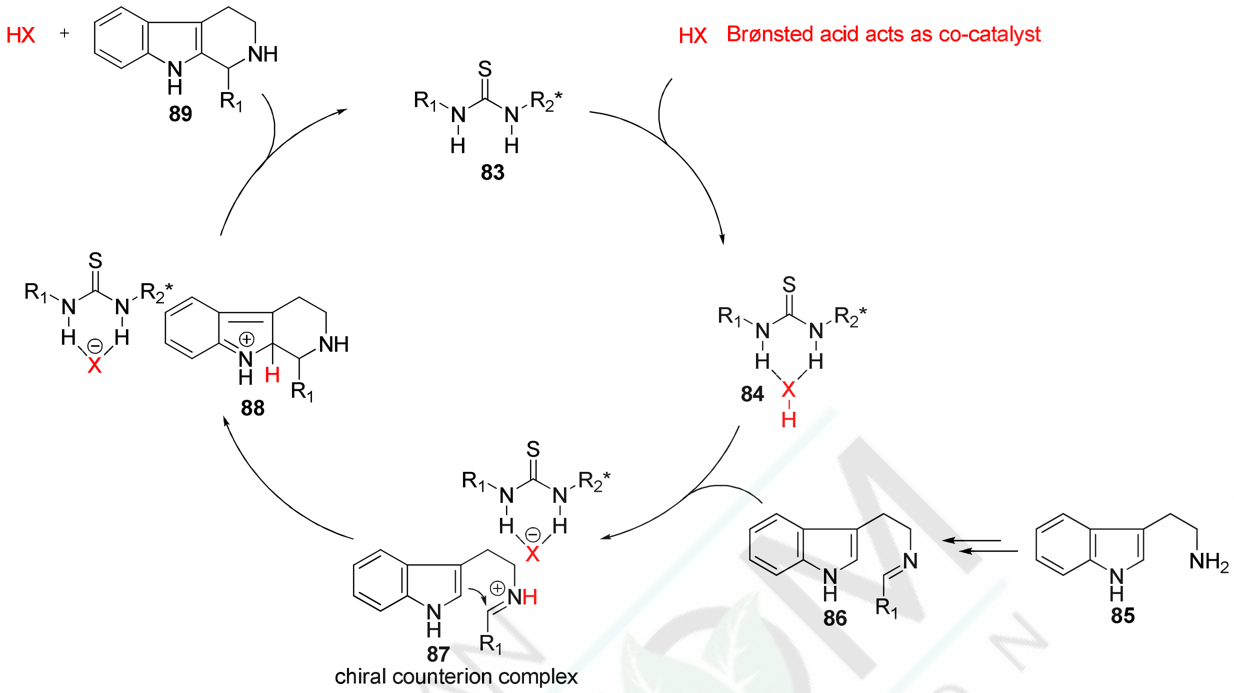


entry	temperature	solvent	drying agents	cat. loading	conversion [%]	*ee* [%]
1	rt	toluene	-	20 mol%	99	89
2	-20°C	toluene	-	20 mol%	99	82
3	0°C	toluene	-	20 mol%	99	80
4	40°C	toluene	-	20 mol%	99	86
5	rt	DCM	-	20 mol%	91	84
6	rt	*n*-dibutylether	-	20 mol%	95	78
7	rt	THF	-	20 mol%	90	63
8	rt	CHCl3	-	20 mol%	90	83
9	rt	toluene	MS 4 Å	20 mol%	99	90
10	rt	toluene	$MgSO_4$	20 mol%	99	92
11	rt	toluene	Na_2SO_4	20 mol%	99	91
12	rt	toluene	-	10 mol%	99	78
13	rt	toluene	-	15 mol%	99	85
14	rt	toluene	-	30 mol%	99	90

Table 5: Optimization of the Pictet-Spengler reaction

2.3.4. *Mechanistic Considerations Towards the Substrate-Catalyst Interaction*

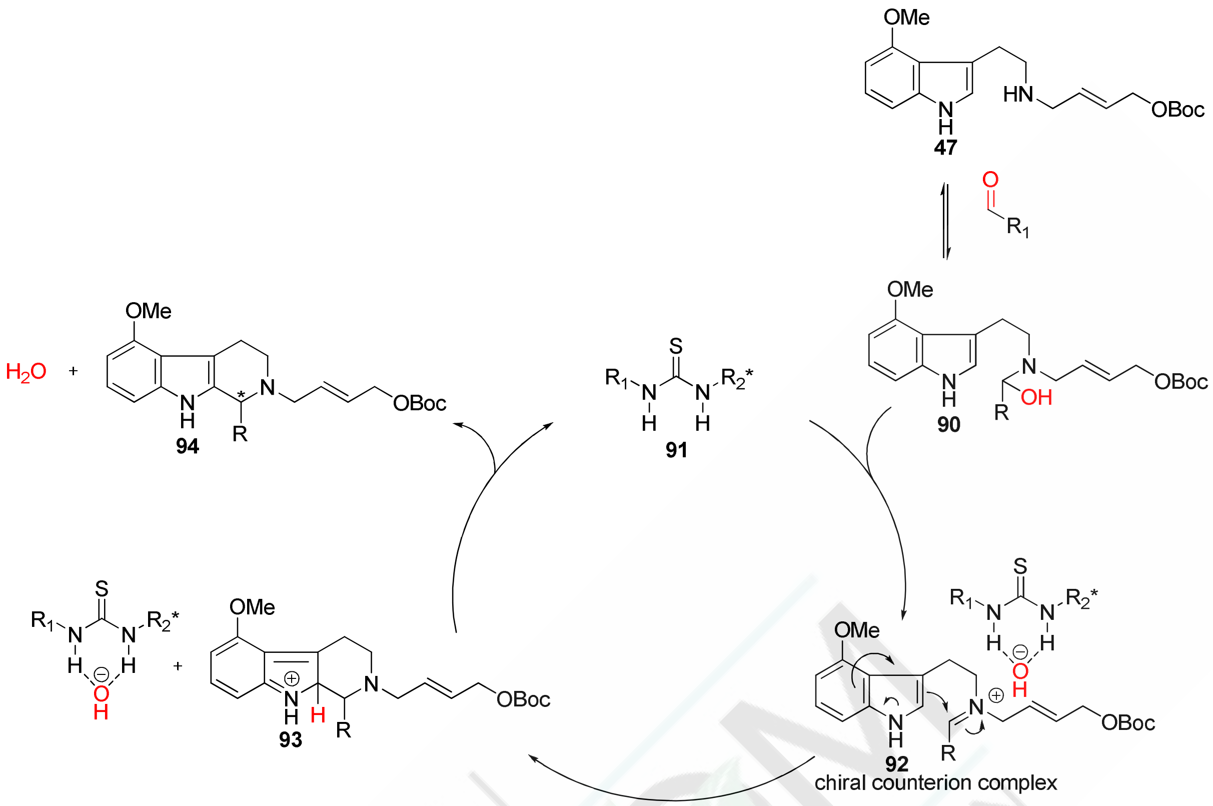
Switching to another catalyst system from BINOL-phosphoric acids to bifunctional *Cinchona* alkaloids carrying a thiourea group implements a completely different interaction between the catalyst and the substrate. While deprotonated phosphoric acids form anion pairs with the iminium ion, this is not possible with a neutral thiourea. In their reports Jacobsen and coworkers formulated a catalytic cycle involving thioureas.[57] In contrast to our substrate Jacobsen used unsubstituted tryptamines which do not carry a substituent on the N_b-nitrogen. Additionally, Jacobsen applied Brønsted acids as co-catalysts which act in combination with the thiourea catalyst. In the first catalytic step, the thiourea is coordinating to the Brønsted acid to form the active species of the catalyst **84** (Scheme 22). When the imine enters the catalytic cycle it is protonated by the catalyst species to from a chiral counter-ion complex **87**. This one consists of the iminium ion and the thiourea carrying the anion of the Brønsted acid via anion-bonding. The thiourea creates a chiral environment in which the ring-closure takes place, similar to the catalysis with phosphoric acids. When the attack occurred, ring-closed product **88** rearomatizes to the tetrahydro-β-carboline **89** with reformation of the Brønsted acid and the thiourea catalyst.



HX +
89
HX Brønsted acid acts as co-catalyst
83
84
88
86
85
87
chiral counterion complex

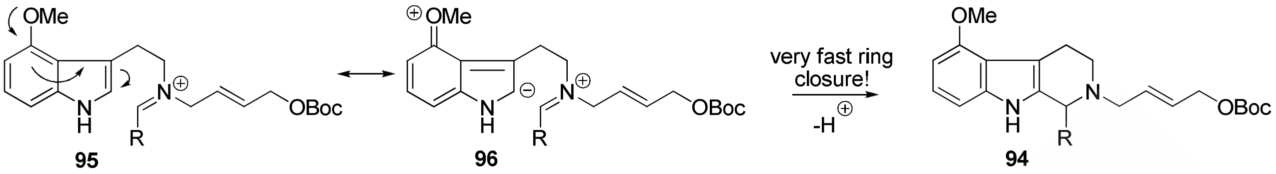
Scheme 22: Proposed catalytic cycle for thiourea catalysts by Jacobsen

Comparing Jacobsen's and our catalytic system, there are certainly differences, but also similarities. The most important difference is the presence of a substituent on the N_b-nitrogen. In contrast to Jacobsen's Pictet-Spengler reaction our substrate does not need to be activated by an acid but by simple secondary iminium ion formation. Our presumption is that the thiourea assists in this imine formation. In our case the imine is formed through abstraction of the hydroxyl anion from hemi-aminal **90**. This abstraction is facilitated by the thiourea via hydrogen-bonding. A chiral counterion-complex is formed resembling the one proposed by Jacobsen. In proximity of the thiourea catalyst ring-closure occurs and after re-aromatization of intermediate **93**, the tetrahydro-β-carboline, the thiourea catalyst and water are formed.



Scheme 23: Proposed catalytic cycle

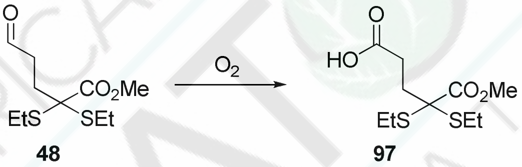
When we deal with the process of thiourea catalysis it is necessary to think about the question why there were such tremendous problems involved with BINOL-phosphoric acid catalysts. Our conjecture is that the explanation could be found if one had a closer look on the rate-determining step of the catalysis. In contrast to the natural products which were successfully synthesized by our group with the help of BINOL-phosphoric acid catalysis (Scheme 16) in this system the indole ring is strongly activated by an electron-donating methoxy group (Scheme 24). Through the strongly nucleophilic indole ring the ring-closure takes place very fast so that it is probably not the ring-closure anymore which is rate-determining, but the formation of the iminium ion. Exactly this formation of the iminium ion is facilitated by a thiourea catalyst (Scheme 23) which gives additional rigidity by two hydrogen bonds. Moreover, the assumption is supported by the fact that molecular sieves catalyzed the reaction as well. This is easy to understand since they support abstraction of the hydroxyl-group from the hemi-aminal through their water-binding properties. To conclude, having the methoxy-group present on the indole ring consequently changes the rate-determining step of the reaction and another catalyst system is required.



Scheme 24: Strong activation through electron-donating methoxy-group

2.3.5. *Necessity of Acid for the Pictet-Spengler Reaction*

During the scale-up of the Pictet-Spengler reaction it was discovered, that a freshly prepared aldehyde resulted in significant lower *ee* and yield as an aldehyde which was made half a year ago and stored in the fridge under argon. The same result was observed when an older batch of aldehyde was columned and used immediately in the reaction. This result was highly surprising since a possible oxidation of the aldehyde over time (Scheme 25) was always considered disadvantageous for the enantioselectivity.[e] In our case however, acid is absolutely required for a good stereoselective reaction.[f]



Scheme 25: Oxidation of the aldehyde

The source of acid can be either partly oxidized aldehyde or added benzoic acid. The results available are of a rather qualitative nature.

An aldehyde batch which was freshly made gave an *ee* of 52% (90% with an old batch) and a yield of 60% (80-90% with and old batch). If the aldehyde was exposed to air for two days at room temperature, the *ee* increased to 66%. Two further days resulted in an *ee* of 81%, when benzoic acid (20 mol%) was added the *ee* was even increased to 88%. Obviously there is a strong dependence between acid and enantioselectivity. A possible reason for this necessity to achieve a selective reaction might be a protonation of the quinuclidine-nitrogen. Through protonation, additional hydrogen is available which can assist in beneficial interaction with

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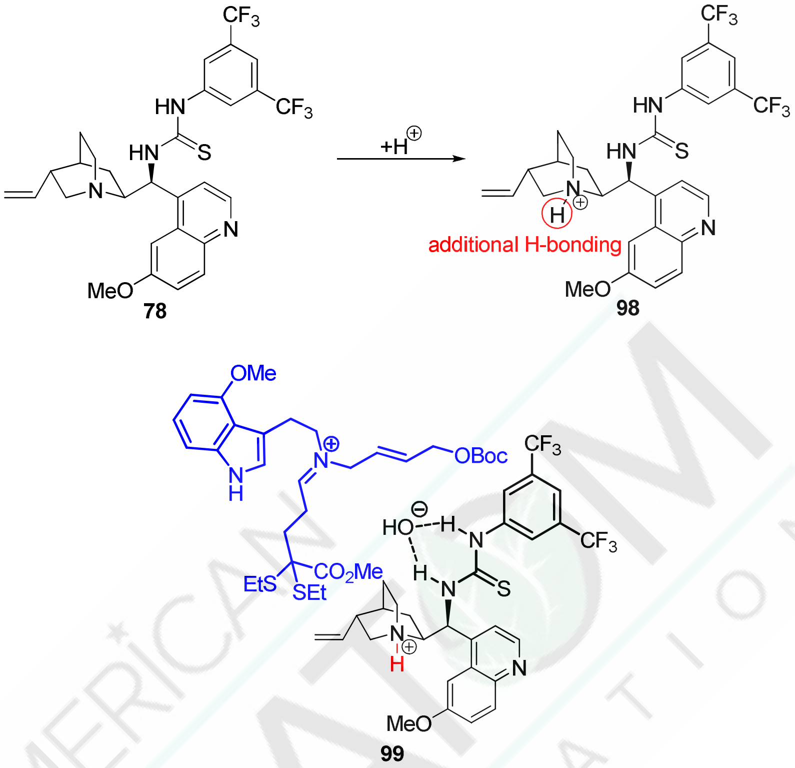
[e] Carboxylic acids are able to catalyze the Pictet-Spengler reaction as well which usually results in a decrease of the *ee*.

[f] Although the aldehyde was stored under argon, the compound surely was exposed to air when the container was opened and closed.

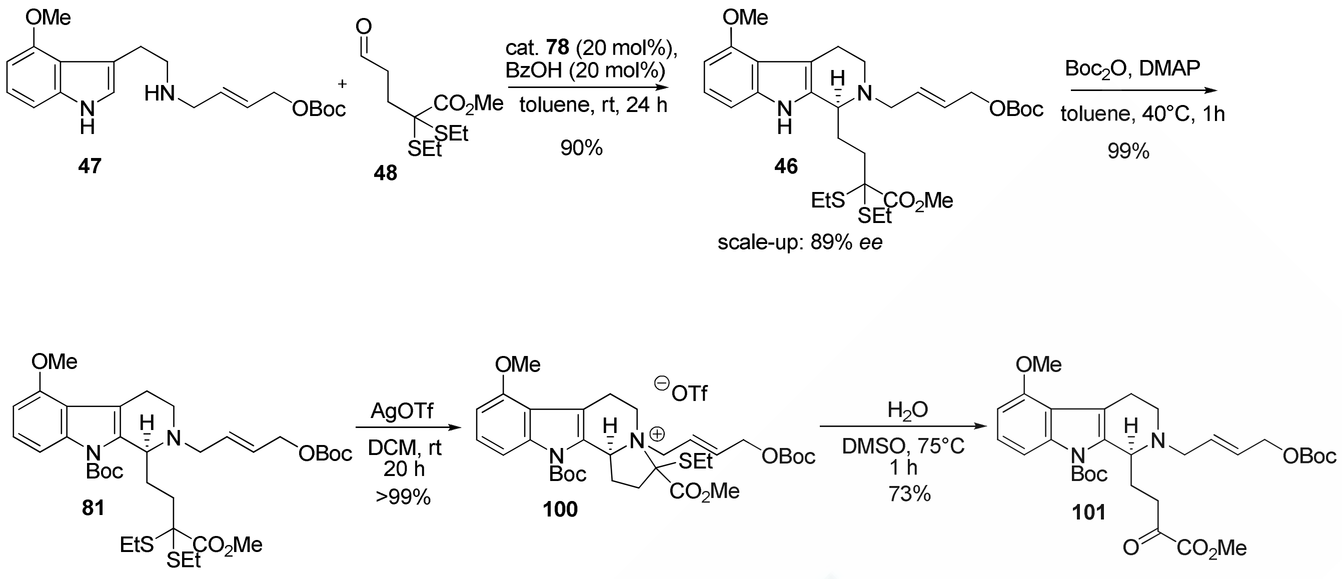
the substrate through hydrogen-bonding (Scheme 26). It is hard to predict with which group the hydrogen-bonding takes place but a possible interaction would be with the abstracted hydroxyl-anion. It is also possible that internal hydrogen binding takes place in the catalyst, forcing the catalyst in a special conformation which is beneficial for the stereoinduction.



Scheme 26: Protonation of the catalyst

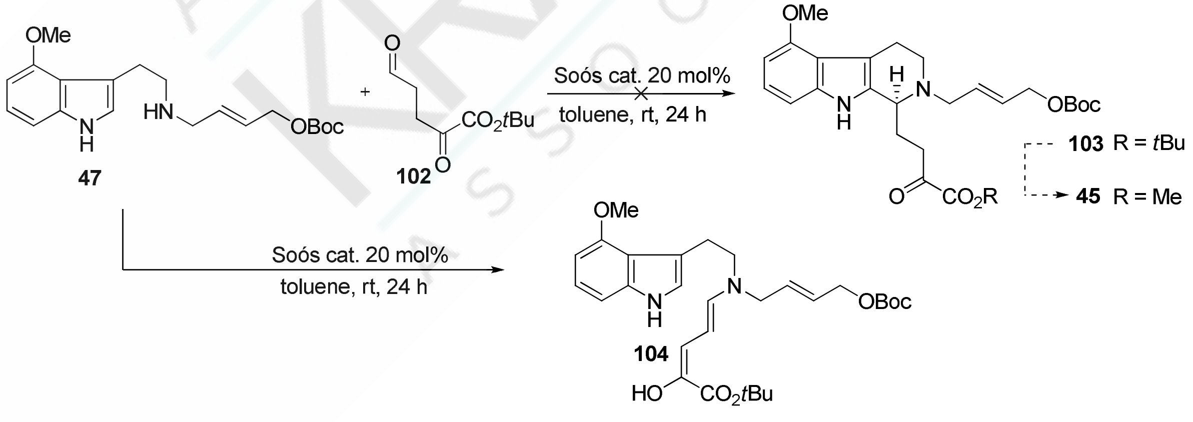
2.4. Synthesis of the α-Keto-Ester

The next step towards the desired corynanthe alkaloids was the deprotection of the thioacetal. At first instance the indole-nitrogen of **46** was protected with a Boc group (Scheme 27). This is necessary since the indole nitrogen is more nucleophilic than the N_b-nitrogen and, unprotected, forms irreversible ring-closure on the α-keto-ester instead the N_b-nitrogen. Additionally, the indole ring is stabilized against oxidation during hydrolysis.[55] Boc-protected tetrahydro-β-carboline **81** is transformed to salt **100** with addition of AgOTf. The salt is hydrolyzed in the next step to give the α-keto-ester.



Scheme 27: Synthesis of the α-keto-ester

To shorten the synthesis it was attempted to use an aldehyde containing the keto-functionality already, so that Boc-protection and the two following steps are not necessary anymore. Previous investigations in our group experienced great instability of the corresponding methyl ester. The analogous *t*Butyl-ester however, promised to be more stable to the conditions and could later be transformed to the desired methyl ester **45**. The aldehyde was applied in the Pictet-Spengler reaction with 20 mol% bifunctional catalyst (Scheme 28).

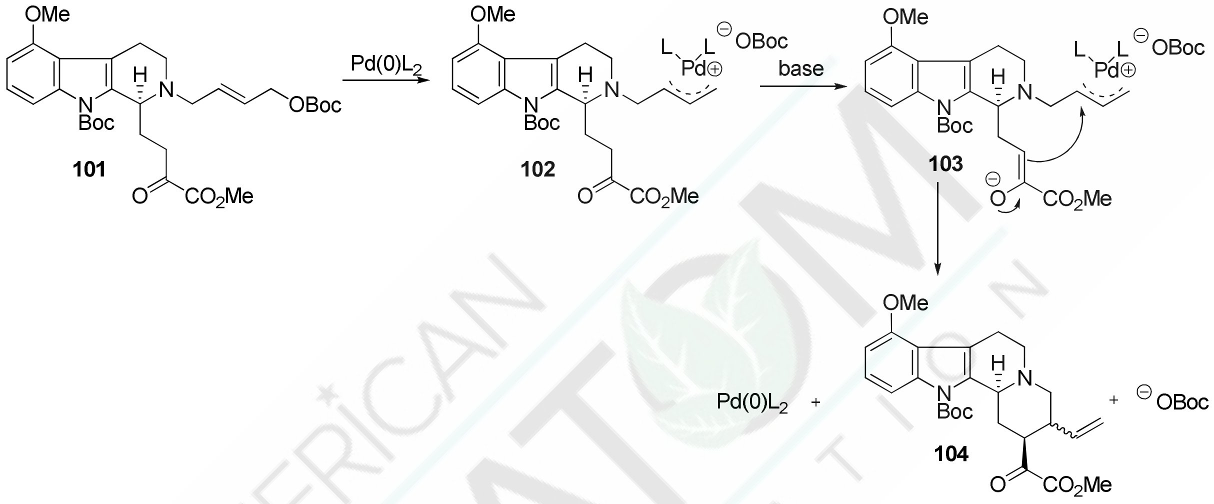


Scheme 28: Pictet-Spengler with α-keto-ester

Unfortunately, instead of the corresponding Pictet-Spengler product **103**, enamine **104** was obtained forming a stable, conjugated and irreversible intermediate. A short cut of the synthesis using aldehydes carrying a keto-group already was therefore not possible.

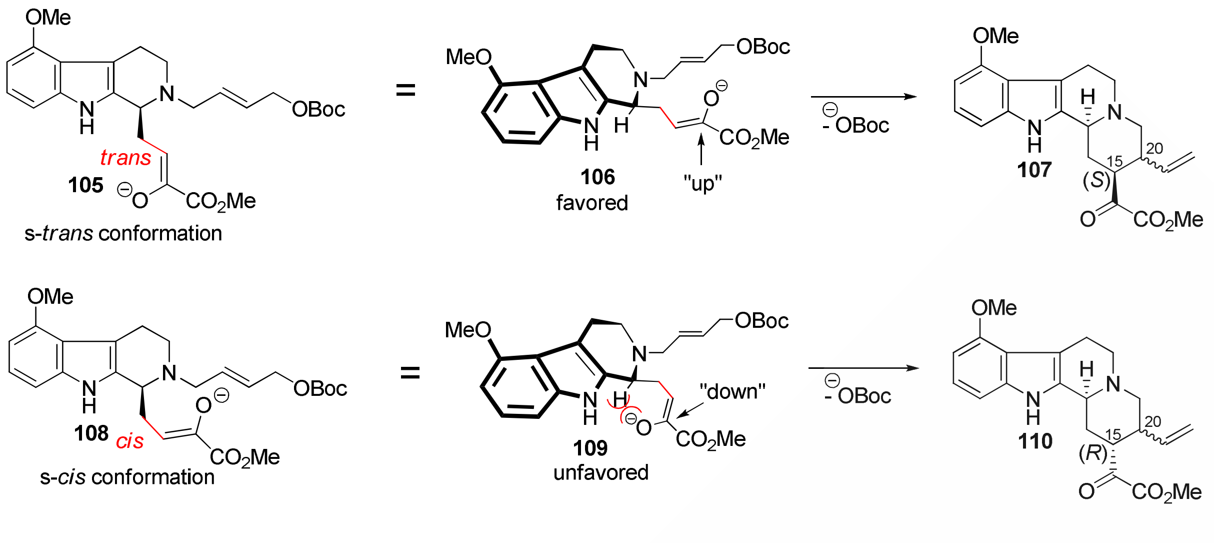
2.5. Tsuji-Trost Allylic Alkylation

The final ring was installed via a Tsuji-Trost allylic alkylation. In general, a palladium complex is added to the alkene which coordinates to the allylic fragment with loss of the OBoc group to from **102** (Scheme 29). A base is added to deprotonate the α-position of the ketone to form the enolate **103** which undergoes nucleophilic attack on the allylic fragment. As a product a six-membered ring bearing a vinyl-substituent is formed.



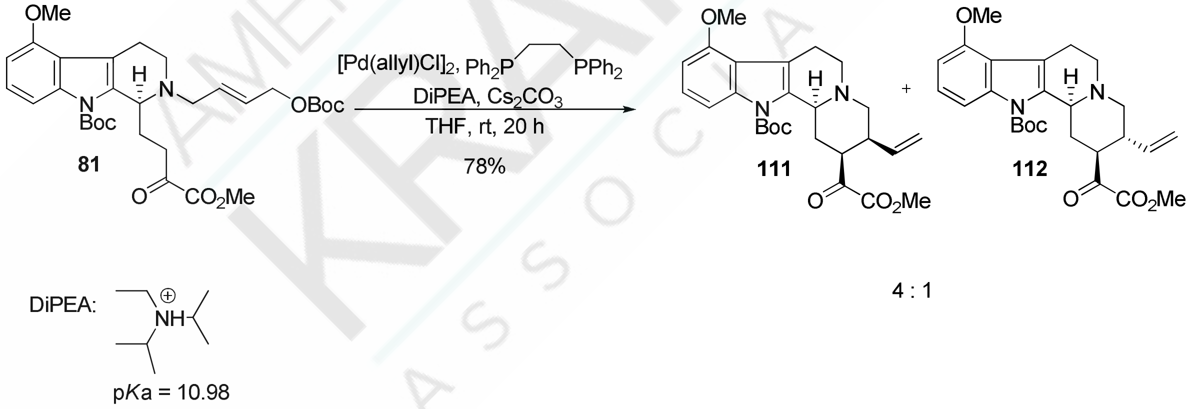
Scheme 29: Mechanism of the Tsuji-Trost allylic alkylation

The stereoselectivity in the reaction is determined by the already existing stereocenter. After formation of enolate **103** there are two conformations possible. The first one having the single bond in a s-*trans* configuration leading to diastereomer **107** and the second one with the single bond in a s-*cis* configuration which results in stereoisomer **110**. In the intermediate with s-*cis* configuration unfavorable steric interactions occur making the formation of isomer **110** rather unlikely. On the other hand, intermediate **106** does not show this unfavorable interaction while having an s-*trans* configuration. Therefore, the formation of isomer **107** is clearly favored and leads to preferred (*S*)-configuration of stereocenter C-15. Influence on stereocenter C-20 is rather difficult since there is no stereoselective induction in close proximity of the substrate available.



Scheme 30: Diastereoselection of stereocenter C-15

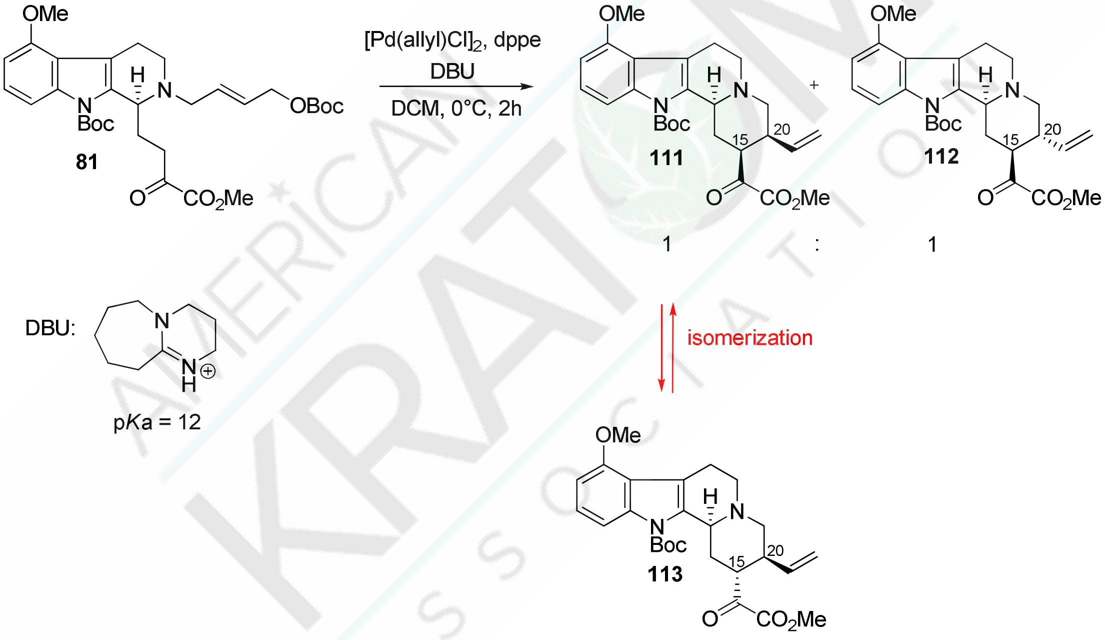
In the reaction we used allylpalladium(II) chloride dimer as the catalyst precursor. The precursor was combined with a bidentate phosphine ligand to from the active catalyst species. As a base, *N*,*N*-diisopropylethylamine (Hünig's base) in combination with Cs_2CO_3 was applied. The reaction gave the two desired diastereomers in a ratio of 4:1 with predominance of the *cis*-isomer which leads to (-)-mitragynine.



Scheme 31: Tsuji-Trost reaction using DiPEA as a base

As another base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used since its basicity is slightly higher and it was expected to change the rate of enolate formation. This possibly changes the ratio between the observed isomers as well (Scheme 32). The resulting ratio was about 1:1 which is favorable because an equal amount of material is obtained to finish both routes towards mitragynine, paynantheine and speciogynine. Unfortunately, a third isomer **113** was observed disturbing the separability of the two favored isomers. Exposing the two isomers **111** and **112** to catalytic amounts of DBU and following the mixtures by NMR revealed that the unfavored isomer was formed from **111** in the basic medium. The *trans*-isomer **112**, however, remained unaffected by addition of base. From that it was concluded that the unwanted isomer is formed through an isomerization process from *cis*-isomer **111** and ends up with inversion of stereocenter C-15. Unfortunately, the structure could not be confirmed analytically, since the isomer was always observed in mixtures with **111** or **112** and never isolated separately.

The attempts to use different ligands with increased bite angles in the reaction with DiPEA did not lead to significant improvement of the *cis*/*trans* ratio. On the contrary, with increased bite angle, the reaction rate decreased significantly and product formation stopped completely at an angle of 111.7° (Xantphos). Dppm with a smaller bite-angle than dppe (72° compared to 85° for dppe) or $P(OMe)_3$ as a monodentated ligand barely resulted in product formation.

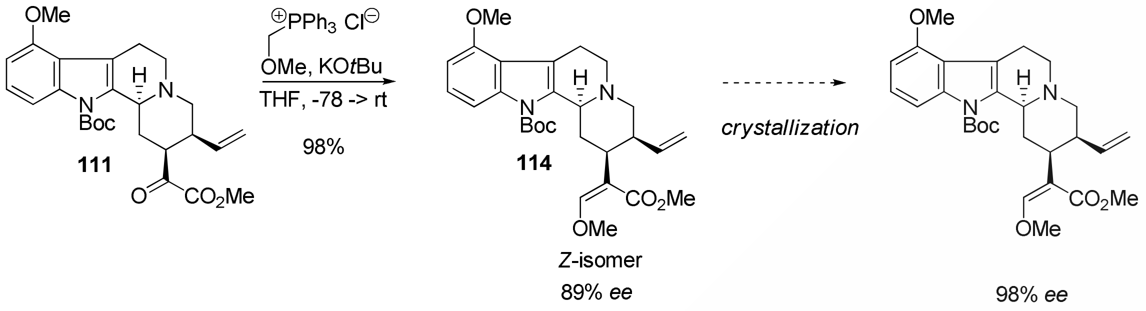


Scheme 32: Tsuji-Trost reaction with DBU as a base

2.6. Final Steps Towards (-)-Mitragynine

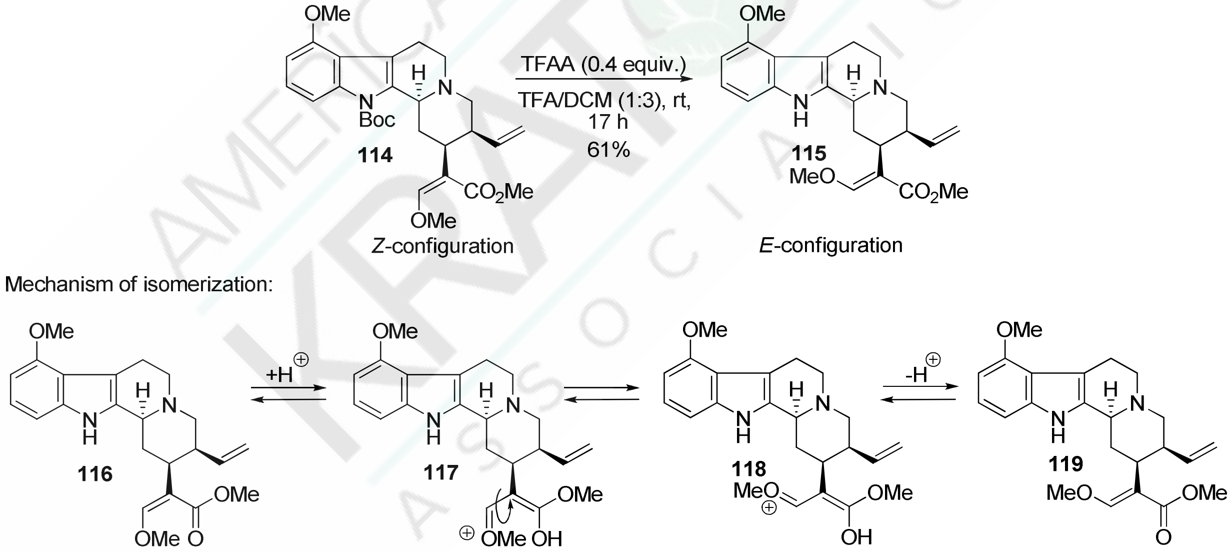
The synthesis towards mitragynine went on with conversion of ketone **111** to enol ether **114**. This was realized with a Wittig reaction using (methoxymethyl)triphenylphosphonium chloride as an ylid-precursor. The reaction was performed in high yield furnishing the *Z*-

isomer as the only product. At this stage partial crystallization of the racemate occurred so that the filtrate was observed with an increased *ee* of 98%.



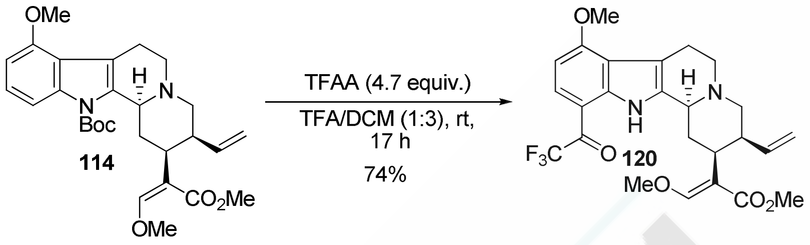
Scheme 33: Synthesis of enol ether **114** leading to mitragynine

To remove the Boc-protecting group on the indolic nitrogen, enol ether **114** was exposed to a TFA/DCM mixture (Scheme 34). Besides deprotection, isomerization of the enol ether to the right configuration took place. Through protonation of the ester to intermediate **117**, the double bond turns into a single bond allowing free rotation. After loss of a proton the thermodynamically more stable *E*-configuration is obtained.



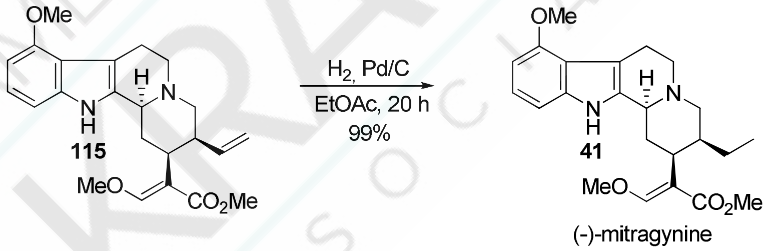
Scheme 34: Isomerization and deprotection of enol ether **114**

To obtain a good yield in the reaction it is important to work very dry and to use high quality TFA. Due to the hygroscopicity of TFA there are traces of water present which easily hydrolyze the enol ether. An attempt to remove traces of water from the reaction was to add the anhydride of TFA (TFAA) to the reaction mixture so that possible water present reacts with the anhydride to form acid again (Scheme 35). Addition of TFAA prevents the hydrolysis of the enol ether very well, but the equivalent of TFAA needs to be chosen carefully. Using an excess of TFAA leads to acylation of the indole ring, yielding the very stable but undesired product **120** (Scheme 35). Through the electron donating methoxy group the substrate is obviously strongly activated and undergoes Friedel-Crafts acylation very easily. This process was prevented if the quantity of TFAA was reduced significantly to catalytic amounts.



Scheme 35: Addition of TFAA to the reaction mixture

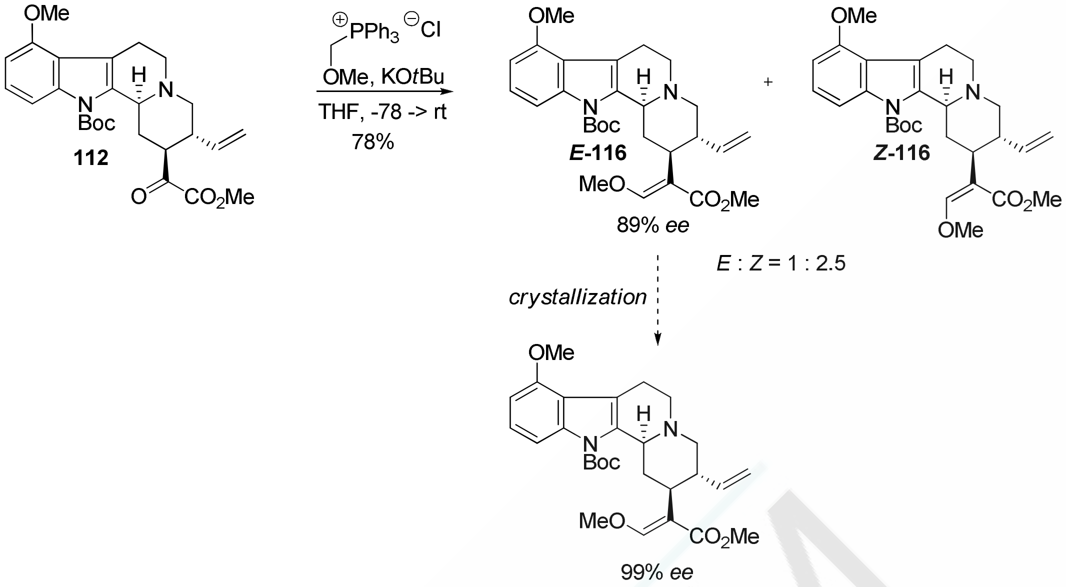
The last step of the synthesis represented hydrogenation of the vinyl-group which went in quantitative yield to furnish (-)-mitragynine in 14 steps, 98% *ee* and an overall yield of 13% from commercially available 4-hydroxyindole.



Scheme 36: Hydrogenation of the vinyl-group

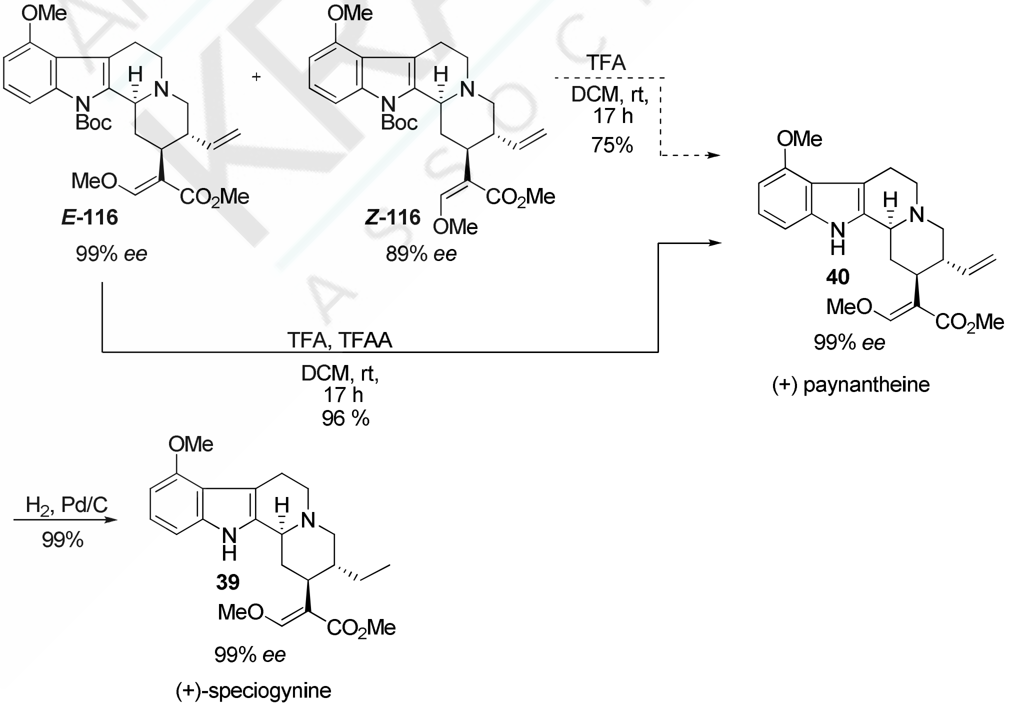
2.7. Final Steps Towards (+)-Paynantheine and (+)-Speciogynine

The synthesis of paynantheine and speciogynine proceeded the same way as for mitragynine. From α-keto ester **112** via a Wittig reaction enol ethers ***E*-116** and ***Z*-116** were synthesized (Scheme 37). To obtain two isomers in this step is at first instance not relevant because both can be used in the next deprotection/isomerization step. For crystallization, however, it was indeed important since a strong difference was observed for the two isomers. Unfortunately, only ***E*-116** was crystallizable to 99% *ee* but with ***Z*-116** neither the racemate nor the enantiomer crystallized. Because of that only the minor isomer observed from the Wittig-reaction was obtained in enantiopure form.



Scheme 37: Wittig reaction of α-keto ester **112**

For the next step both products ***E*-116** and ***Z*-166** can be used synthesize paynantheine which was performed with racemic material in 75% yield. To yield the end-products in high *ee*, the reaction was repeated only with ***E*-116** which was crystallized to 99% *ee*. Using TFA and catalytic amounts of TFAA furnished paynantheine in 13 steps and an overall yield of 4.3%. The last step towards speciogynine was realized through hydrogenation.

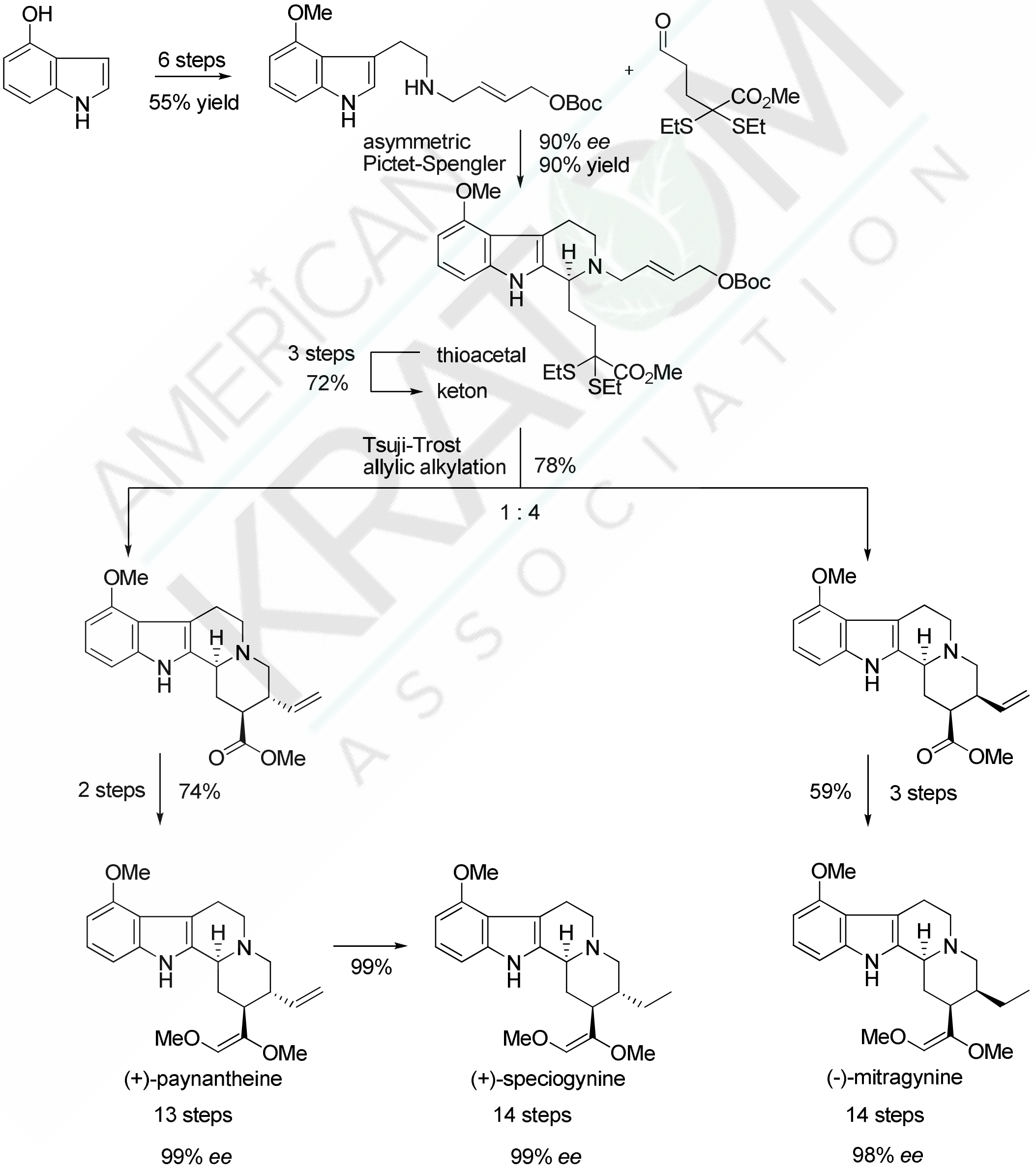


Scheme 38: Deprotection and isomerization towards paynantheine and speciogynine

3. Conclusion

3.1. Summary

Within the scope of this thesis, the enantioselective total synthesis of the three natural products mitragynine, paynantheine and speciogynine was realized. Over an asymmetric Pictet-Spengler reaction an *ee* of 90% (89% scale-up) was introduced in the route which was later increased by crystallization.



Scheme 39: Summary of the synthesis towards mitragynine, paynantheine and speciogynine

After a Tsuji-Trost reaction two diastereomers were obtained each leading to the natural products mitragynine or paynantheine and speciogynine. Mitragynine was made in 14 steps with an *ee* of 98% in the final product. Paynantheine and speciogynine were synthesized with an *ee* of 99%.

3.2. Comparison with Other Syntheses

To formulate a precise comparison of our synthesis of (-)-mitragynine with the already published routes (presented in the introduction: section 1.4) is rather difficult because the overall aim of research has been different in each case. However, I will try to point out some characteristics of each synthesis and ours. When Takayama published the first synthesis, the focus was not to develop the most efficient way but to make the molecule in first instance. Using enzyme-catalyzed hydrolysis of an acetate, an enantiopure alcohol was obtained. The synthesis is relatively short, but the observed yields remain rather low, so that an overall yield of 3% is obtained for 9 steps[a] compared to 13% yield with our synthesis. Although the enantiodetermining step results in higher *ee* than our organocatalyzed Pictet-Spengler reaction, enzymes always feature limited substrate specificity and the question of availability arises. For the biological evaluation of unnatural derivatives, the synthetic use of enzymes might be problematic. Our catalyst on the contrary allows more substrate-flexibility and is based on the *Cinchona* bark, a cheap and renewable resource. The synthesis by Cook published 14 years later envisioned the synthesis of several natural products applying a chiral auxiliary strategy. From an intermediate in the synthesis several natural products including mitragynine were reached. Although the observed enantioselectivity of the asymmetric step was higher than with our Pictet-Spengler reaction (95% *ee* compared to 90% *ee*), we were able to exceed the enantiomeric purity of the final product later by crystallization. Overall, Cooks synthesis is significantly longer than ours (23 steps compared to 14), unfortunately the overall yield could not be determined due to missing information about the yields of single steps. The most recent published formal synthesis by Ma *et al.* uses an organocatalytic approach. A lower *ee* of 81% was achieved in the scale-up and the synthesis was not finished, so that the overall yield could not be determined.

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[a] Synthesis of bromine **5** not included.

3.3. Conclusion

The synthesis of (-)-mitragynine, (+)-paynantheine and (+)-speciogynine has been realized using an organocatalytic Pictet-Spengler reaction. It is therefore the first completed synthesis of mitragynine using organocatalysis and the first synthesis of paynantheine and speciogynine in general. With our route, new analogues can be synthesized which might show increased or different biological activity.

Additionally, we developed the first Pictet-Spengler reaction catalyzed by a bifunctional organocatalyst reaching an *ee* of 90%. Strongly activated substrates with electrondonating substituents on the indole system might not be catalyzed by BINOL-phosphoric acids. In these cases, a bifunctional catalyst bearing a thiourea might be a possible solution. This turns the class of bifunctional *Chincona* alkaloids to a new attractive catalyst species for the Pictet-Spengler reaction on which further research is worthwhile.

4. Abbreviations

Ac	acetyl
aq.	aqueous
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butylcarbonyl
b.p.	boiling point
bs	broad signal (NMR)
Bu	butyl
Bz	benzoyl
cat.	catalyst
d	doublet (NMR)
d	day(s) (reaction)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DiPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopydridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,2-bis(diphenylphosphino)methane
E	entgegen
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl
h	hours
Hz	Hertz

HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
IR	infrared
L	ligand
LAH	lithium aluminium hydride
LDA	lithium diisoproylamine
m	*meta*
m	multiplet (NMR)
Me	methyl
min	minute(s)
MP	melting point
MS	molecular sieves
ND	not determined
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	nosyl
o	*ortho*
p	*para*
ppm	parts per million
PE	petroleum ether
Ph	phenyl
rt	room temperature
s	singlet (NMR)
t	*tert*
t	triplet (NMR)
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Z	zusammen

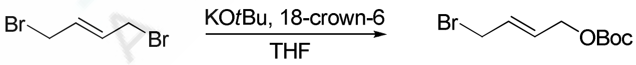
5. Experimental

General remarks:

All ^{1}H-NMR and ^{13}C-NMR (APT) spectra were recorded with a Bruker Avance 400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) at room temperature. IR spectra were obtained using a Bruker IFS 28 FT-spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical thin layer chromatography was performed using Merck TLC plastic roll 500 x 20 cm silica gel F_{254}. Flash chromatography was carried out on Biosolve 60 Å (0.032 – 0.063 mm) silica gel. *Ee*s were determined on Chiracel® OD-H (Chiral Technologies Europe, 0.46 cm x 25 cm) columns. Melting points were measured with a Leitz-Wetzlar melting point microscope and are uncorrected. Mass spectra and accurate mass measurements were performed using a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer.

All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone. Toluene was stored under 4 Å molecular sieves. Commercial reagents and solvents were purchased from Biosolve, Sigma-Aldrich, Fluka or Acros and used as received. 4-hydroxy-indole was purchased from AK Scientific Inc. (100g, 215 $). Powdered 4 Å molecular sieves (Fluka) were dried at 200°C and 0.1 mbar.

(E)-4-bromobut-2-enyl *tert*-butyl carbonate



11 g (0.1 mol) KO*t*Bu and 0.5 g 18-crown-6 was dissolved in 250 mL anhydrous DMSO. A CO_2-stream generated from dry ice was directed through the solution with two thick needles and the mixture was stirred with a mechanical stirrer for 1 h. After formation of a thick gel, 21.4 g (0.1 mol) of 1,4-dibromobutene dissolved in 40 mL THF was given to the mixture in one portion. After 2 h of stirring the reaction was quenched with half saturated NH_4Cl solution. The layers were separated and the aqueous phase was extracted with Et_2O (3x). The organic layers were combined and washed with water (2x) and the organic phase was dried

with $MgSO_4$ and the solvents evaporated. A column of thickness: 66 mm and length: 150 mm was packed with EtOAc:PE, 6:94; Eluent EtOAc:PE, 6:94 (1L) and EtOAc:PE, 8:92 (1L). The product was isolated as a colorless oil.

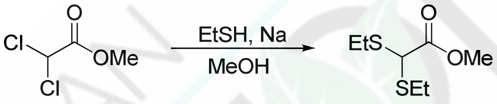
Yield: 43% (10.9 g, 0.043 mol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.02 (m, 1H), 5.90 (m, 1H), 4.60 (d, 2H, J=5.70 Hz), 3.97 (d, 2H, J=7.40 Hz), 1.51 (s, 9H) ppm.

For the remaining analytical data see:

M. J. Wanner, E. Claveau, J. H. Van Maarseveen, H. Hiemstra, *Eur. J. Org. Chem.* **2011**, *17,* 13680-13683.

methyl 2,2-bis(ethylthio)acetate



58

4.6 g (0.2 mol) sodium was placed in a three-neck flask with a dropping funnel and a condenser under nitrogen-atmosphere. The flask was chilled in an ice-bath and 100 mL of methanol was added slowly. When the sodium dissolved completely, 15 mL (0.2 mmol) ethanethiol was added dropwise. The ice bath was removed and 10.39 mL (0.1 mol) methyl dichloroacetate was slowly given to the mixture and the suspension was stirred for 48 h at room temperature. The mixture was quenched with 75 mL H_2O and 150 mL of diethyl ether. The ether layer was separated and washed with water (50 mL) and saturated NaCl solution (50 mL). The organic phase was dried over $MgSO_4$, the solvent removed and the resulting oil purified by distillation: 60°C ($1.4 \cdot 10^{-1}$ Torr); Lit: 125-127°C (5 Torr).

Yield: 87% (16.87 g, 0.087 mol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.40 (s, 1H), 3.80 (s, 3H), 2.74 (m, 4H), 1.30 (t, 6H, J=7.43 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 13.9, 24.9, 49.8, 52.5, 169.5 ppm.

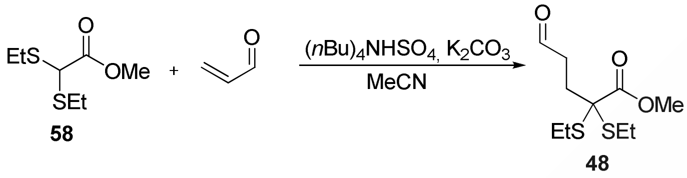
IR: ν = 2967, 2929, 1731, 1434, 1260, 1137 cm^{-1}.

For the remaining analytical data see:

L.M. Lerner, *J. Org Chem.* **1976**, *41*, 2228-2229.

Synthesis of aldehyde 48

Michael-addition



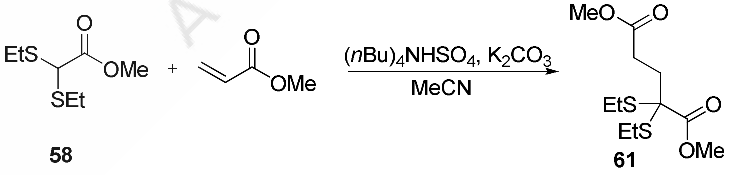
2.91 g (15 mmol) of methyl 2,2-bis(ethylthio)acetate was dissolved in 50 mL of acetonitrile. 8.29 g (60 mmol) finely powdered potassium carbonate and 0.255 g (0.75 mmol) tetrabutylammonium hydrogen sulfate was given to the mixture. Then, freshly distilled acrolein was added in two portions one at the beginning of the reaction (2.5 mL, 38.5 mmol) and one after 30 min (2.5 mL, 38.5 mmol). The suspension was stirred at room temperature for 1 h in total. The inorganic solid was removed by filtration, the solvent evaporated and the mixture purified via column chromatography (EtOAc:PE, 1:4/1:3). The product was obtained as a colorless oil.

Yield: 29% (1.09 g, 4.35 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.83 (s, 1H), 3.80 (s, 3H), 2.64 (m, 2H), 2.73 (m, 4H), 2.34 (m, 2H), 1.24 (t, 6H, J=7.5 Hz) ppm.

For the remaining analytical data see:

J. Gonzalez, F. Sánchez, T. Torres, *Synthesis*, **1983**, *911-913*.



0.969 g (5 mmol) of methyl 2,2-bis(ethylthio)acetate was dissolved in 16 mL of acetonitrile. 2.76 g (20 mmol) of finely powdered K_2CO_3 salt and 0.085 g (0.25 mmol) of tetrabutylammonium hydrogen sulfate was added. 0.5 mL (5.5 mmol) of methylacrylate was given to the mixture and the suspension was stirred at 80°C for 90 min. The inorganic salts were filtered and washed with acetonitrile. The solvent was evaporated and the product obtained as a colorless oil via distillation. b.p. 104°C, $8{\cdot}10^{-1}$ Torr.

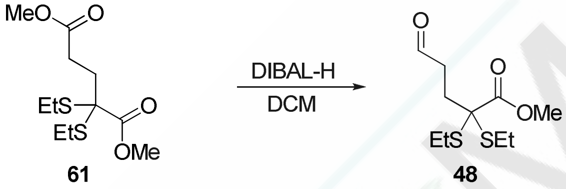
Yield: 66% (0.9538 g, 3.40 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.80 (s, 3H), 3.70 (s, 3H), 2.65 (m, 4H), 2.57 (m, 1H), 2.34 (m, 1H), 1.24 (t, 6H, J=7.51) ppm.

For the remaining analytical data see:

J. Gonzalez, F. Sánchez, T. Torres, *Synthesis*, **1983**, *911-913*.

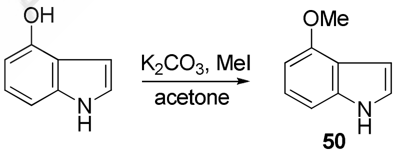
DIBAL-H reduction



0.954 g (3.40 mmol) **61** was dissolved in 14 mL DCM and the solution was cooled to -78°C. 3.74 mL (3.74 mmol) of DIBAL-H as a 1M solution in hexane was slowly added and the mixture was stirred for 2 h at -78°C. The reaction was quenched with methanol and 16 mL of saturated potassium sodium tartate solution (Rochelle salt). The mixture was stirred vigorously for 30 min. The layers were separated and the aqueous phase was washed with DCM (4x). The organic layers were combined and the solvent removed. Column chromatography with EtOAc:PE 1:4/1:3 furnished the product as a colorless oil.

Yield: 70% (0.5934 g, 2.37 mmol)

4-methoxy-1H-indole



44.9 g (325 mmol) K_2CO_3 and 28.4 g (200 mmol) MeI were added to a solution of 13.31 g (100 mmol) 4-methoxy-1H-indole in 200 mL acetone. The suspension was stirred under reflux for 48 h and at room temperature for further 48 h. The mixture was filtered over celite and the solvent evaporated. Due to limited solubility of the mixture in the eluent, the compound was absorbed on silica gel during evaporation. Purification through flash chromatography using (EtOAc:PE, 1:2) gave the product as white crystals.

Yield: 89% (13.068 g, 89 mmol)

Melting point: 64 – 67 °C

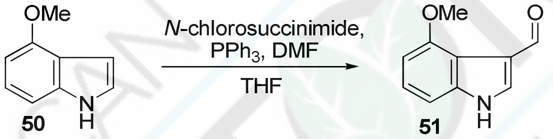
^{1}H-NMR (400 MHz) δ = 8.16 (s, 1H), 7.37 (t, 1H, J=8.0Hz), 7.11 (m, 2H), 6.93 (t, 1H, J=2.6Hz), 6.77 (d, 1H, J=7.8Hz), 4.14 (s, 3H) ppm.

^{13}C-NMR (100 MHz) δ = 153.2, 137.1, 122.6, 122.6, 118.4, 104.4, 99.5, 99.4, 55.2 ppm.

IR: ν = 3408, 1615, 1588, 1502, 1464, 1439, 1361 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_9H_{10}ON$: 148.0718; found: 148.0770.

4-methoxy-1H-indole-3-carbaldehyde



40.1 g (153 mmol) triphenylphosphine was dissolved in 640 mL dry THF and 20.41 g (153 mmol) *N*-chlorosuccinimide was added in portions. The suspension was stirred vigorously for 30 min at room temperature. Then, 23.5 mL (306 mmol) DMF was added to the reaction and the mixture was stirred under reflux for 1 h. Further, 7.5 g (51 mmol) indole was added and the mixture was stirred under reflux for 1 h. The reaction mixture was cooled down to room temperature and the THF was evaporated. 640 mL H_2O was added to the mixture and it was stirred under reflux for 1 h. The mixture was cooled down and basified with 10% NaOH. The aquaous phase was extracted with 200 mL (4x) EtOAc and the organic layers combined and evaporated. Column chromatography with EtOAc:PE, 1:1 gave the product as orange crystals.

Yield: 81% (7.239 g, 41.3 mmol)

Melting point: 151-154°C

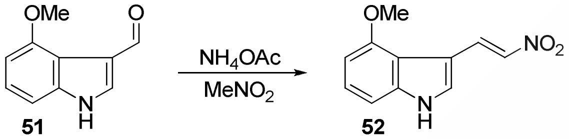
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.53 (s, 1H), 8.79 (s, 1H), 7.95 (d, 1H, J=3.07 Hz), 7.24 (t, 1H, J=8.07), 7.10 (d, 1H, J=8.17 Hz), 6.75 (d, 1H, J=7.85 Hz), 4.03 (s, 3H) ppm

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 187.6, 153.7, 137.6, 128.4, 123.1, 118.3, 115.6, 105.3, 101.6, 54.8 ppm.

IR: ν = 3246, 1648, 1463, 1386, 1363, 1328 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{10}H_{10}O_2N$:176.0667; found: 176.0712.

(E)-4-methoxy-3-(2-nitrovinyl)-1H-indole



1.76 g (22.8 mmol) NH_4OAc and 2.0 g (11.4 mmol) aldehyde were dissolved in 67 mL nitromethane and the suspension was heated under reflux for 1 h. The mixture was cooled down to room temperature and the solvent evaporated. The solid was dissolved in a small amount of methanol and precipitated slowly with water. The solid was filtrated over celite and dried under vacuum. The product was obtained as a red solid.

Yield:	96% (2.3985 g, 10.99 mmol)
Melting point:	185-188 °C

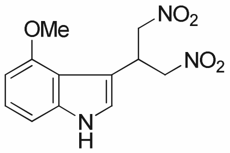
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.67 (bs, 1H), 8.52 (d, 1H, J=13.38 Hz), 7.98 (d, 1H, J=13.38), 7.61 (d, 1H, J=2.73), 7.25 (d, 1H, J=8.04), 7.07 (d, 1H, J=8.19 Hz), 6.712 (d, 1H, J=7.92 Hz), 4.04 (s, 3H) ppm.

^{13}C-NMR (100 MHz, CDCl3) δ = 152.9, 138.4, 134.5, 131.9, 130.5, 123.5, 114.4, 107.9, 105.1, 101.3, 54.3 ppm.

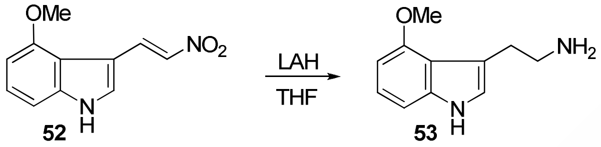
IR: ν = 3285, 2940, 1687, 1612, 1511, 1481, 1440, 1304 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{11}H_{11}O_3N_2$: 219.0725, found: 219.0773.

Remark: When the mixture is stirred too long, deprotonated nitromethane adds to the double bond of the product to form the di-nitro-substituted product.



2-(4-methoxy-1H-indol-3-yl)ethanamine

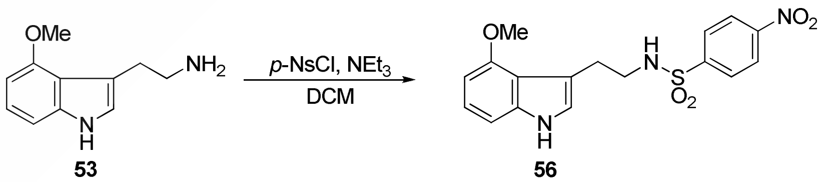


58.53 g (225 mmol) LAH was dissolved in 90 mL of dry THF and cooled to 0°C. 4.456 g (20.4 mmol) (E)-4-methoxy-3-(2-nitrovinyl)-1H-indole was dissolved in 220 mL dry THF and given to the mixture with a dropping funnel. After 3 h of reflux the flask was placed in an ice bath and first water (1.3 g / g $LiAlH_4$), then 15% aqueous NaOH (1.3 g / g $LiAlH_4$) and finally again water (3.25 g / g $LiAlH_4$) was carefully added with a dropping funnel. The mixture was stirred vigorously for 15 min and filtrated. The residue was washed with Et_2O (5x) and the combined organic layers evaporated. The product was obtained as a brown solid.

Yield:	99% (3.848 g, 20.2 mmol)
Melting point:	110-105°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.06 (bs, 1H), 7.11 (t, 1H, J=7.95 Hz), 6.99 (d, 1H, J=7.70 Hz), 6.91 (d, 1H, J=2.15 Hz), 6.51 (d, 1H, J=7.74 Hz), 3.94 (s, 3H), 3.03 (s, 4H) ppm.
^{13}C-NMR (100 MHz) δ =154.4, 138.1, 122.1, 121.2, 116.9, 112.9, 104.5, 98.7, 54.7, 42.8, 30.6 ppm.
IR: δ = 2932, 1585, 1507, 1463, 1436, 1361 cm^{-1}.

N-(2-(4-methoxy-1H-indol-3-yl)ethyl)-4-nitrobenzenesulfonamide



2.25 mL (16.1 mmol) triethylamine was added to a solution of 2.55 g (13.4 mmol) amine **53** in 50 mL DCM. The mixture was cooled down to 0°C and 3.27 g (14.7 mmol) *p*-nitro-tosylchloride was added in portions. The suspension was stirred for 2 h at 0°C. The mixture was extracted with H_2O (2x) and sat. $NaHCO_3$ (1x) solution. The organic layers were combined and the compound was absorbed on silica gel. Column chromatography with EtOAc:PE, 1:2/1:1 gave the product as an orange solid.

Yield: 87% (4.37 g, 11.6 mmol)

Melting point: 136-140 °C

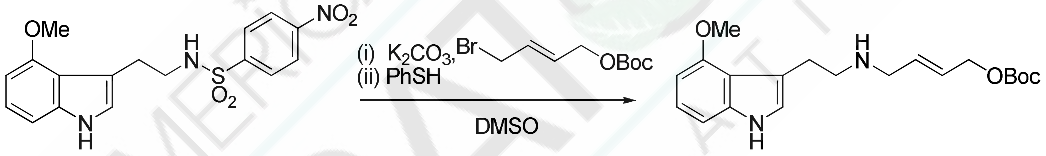
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.89 (m, 2H), 7.54 (m, 2H), 7.08 (t, 1H, J=7.99 Hz), 6.88 (d, 1H, J=8.18 Hz), 6.76 (d, 1H, J=2.31 Hz), 6.46 (d, 1H, J=7.78 Hz), 3.92 (s, 3H),3.40 (m, 2H), 3.00 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 153.2, 148.2, 145.3, 137.6, 126.7, 122.6, 121.3, 121.5, 116.1, 110.6, 104.5, 98.2, 54.4, 44.1, 26.1 ppm.

IR: ν = 3406, 1528, 1349 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{17}H_{18}O_5N_3S$: 376.0922; found: 376.0971.

(E)-*tert*-butyl 4-(2-(4-methoxy-1H-indol-3-yl)ethylamino)but-2-enyl carbonate



56 **47**

4.10 g (29.7 mmol) of finely powdered K_2CO_3 and 2.73 g (10.9 mmol) bromoalkene were added to a solution of 3.71 g (9.9 mmol) *N*-(2-(4-methoxy-1H-indol-3-yl)ethyl)-4-nitrobenzenesulfonamide in 33 mL DMSO. After stirring for 4 h at room temperature 3.0 mL (29.7 mmol) of thiophenol was given to the mixture. After 2 h the reaction was quenched with water and the aqueous phase was extracted with EtOAc/NH_4Cl. The organic layers were combined and washed with water (3x). After removal of the solvent the mixture was purified by column chromatography (EtOAc:PE, 1:1; EtOAc; MeOH:EtOAc, 1:9; EtOAc with 5% MeOH and 5% NEt_3). The product was obtained as a brown highly viscous oil.

Yield: 94% (3.35 g, 9.3 mmol)

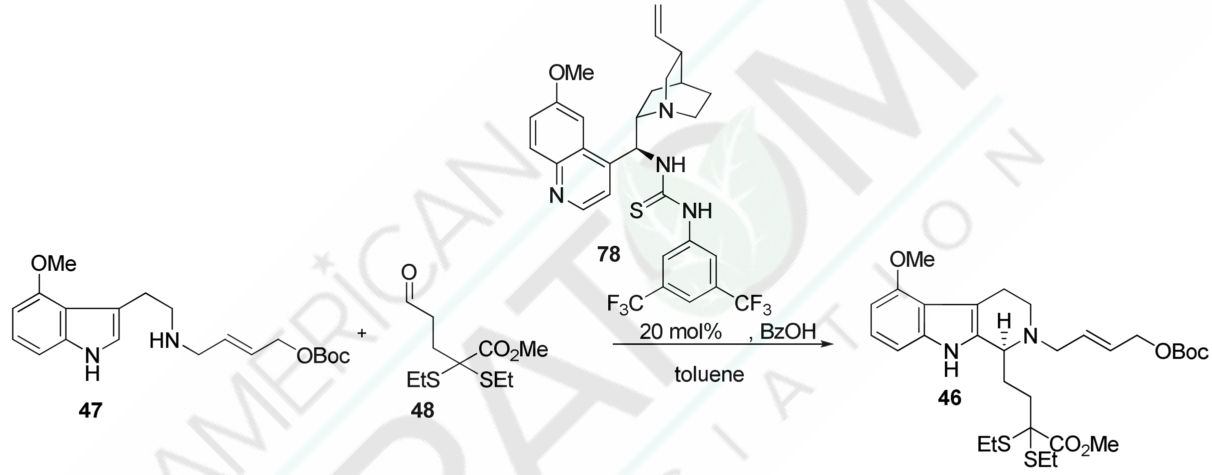
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.64 (bs, 1H), 7.09 (t, 1H, J=7.95 Hz), 6.95 (d, 1H, J=8.14 Hz), 6.87 (s, 1H), 6.49 (d, 1H, J=7.72 Hz), 5.73 (m, 1H), 5.87 (m, 1H), 4.51 (d, 2H, J=6.2Hz), 3.92 (s, 3H), 3.30 (d, 2H, J=5.86 Hz), 3.10 (t, 2H, J=6.74 Hz), 2.97 (t, 2H, J=6.74 Hz), 1.50 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 154.6, 153.2, 138.1, 133.5, 125.3, 122.5, 121.1, 117.1, 113.6, 104.5, 99.1, 81.9, 66.9, 54.9, 50.5, 50.1, 27.6, 26.9 ppm.

IR: ν = 2932, 1740, 1368 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{20}H_{29}O_4N_2$: 361.2083; found: 361.2122.

Organocatalyzed Pictet-Spengler reaction



0.033 g (0.055 mmol) of catalyst and 0.0067 g (0.055 mmol) benzoic acid was added to a solution of 0.1 g (0.277 mmol) tryptamine **47** in 5 mL of toluene. Next, 0.083 g (0.33 mmol) of aldehyde was given to the mixture and the reaction was stirred for 24 h at room temperature. The solvent was evaporated and the resulting oil purified by column chromatography using EtOAc:DCM:PE, 1:4:4. The product was observed as a colorless oil.

Yield:	90% (0.147 g, 0.25 mmol)	
ee:	89%	
Optical rotation:	$[\alpha]_D^{20}$ = -19.6° (c = 1.03, $CHCl_3$)	
HPLC:	major enantiomer	18.22 min
	minor enantiomer	23.40 min
	(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 90:10, flow: 0.6 mL/min)	

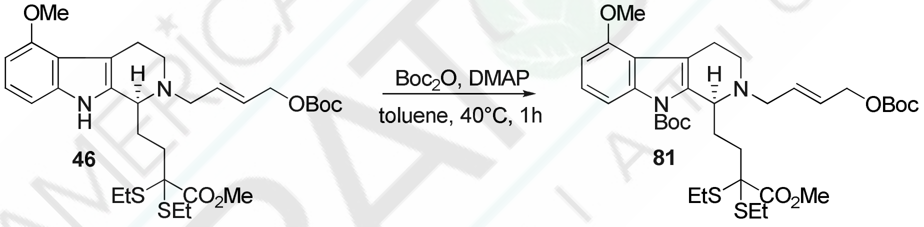
^{1}H-NMR (400 MHz, CDCl$_3$) δ = 7.79 (bs, 1H), 7.04 (t, 1H, J=7.9 Hz), 6.94 (d, 1H, J=8.0 Hz), 6.49 (d, 1H, J=7.6 Hz), 5.91 (m, 1H), 5.76 (m, 1H), 4.58 (d, 2H, J=6.1Hz), 3.91 (s, 3H), 3.78 (s, 3H), 3.67 (t, 1H, J=5.5Hz), 3.34 (dd, 1H, J=6.0 Hz, J=14.1Hz), 3.17 (m, 2H), 3.00 (m, 1H), 2.82 (m, 2H), 2.58 (m, 4H), 2.09 (m, 2H), 1.97 (m, 2H), 1.52 (s, 9H), 1.21 (dt, 6H, J=7.5 Hz, J=13.8 Hz) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$) δ = 171.3, 154.3, 153.3, 137.1, 133.6, 132.3, 126.4, 122.0, 117.2, 108.5, 104.2, 99.6, 82.1, 67.0, 65.0, 56.4, 55.2, 54.6, 53.0, 46.0, 32.0, 29.1, 27.8, 24.0, 23.4, 20.6, 13.6, 13.3 ppm.

IR: ν = 3393, 2931, 1723 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{30}H_{45}N_2O_6S_2$: 593.2674; found: 593.2722.

Boc-protection of 46



0.37 g (1.70 mmol) di-*tert*-butyl dicarbonate and 0.035 g (0.28 mmol) DMAP was added to a solution of 0.673 g (1.13 mmol) tetrahydro-*β*-carboline **46** in 20 mL toluene. The mixture was heated to 40°C and stirred for 1 h. Conversion was checked on TLC. The solvent was evaporated and the product isolated via column chromatography using EtOAc:DCM:PE = 1:4:4.

Yield:	99% (0.779 g, 1.12 mmol)	
ee:	89%	
Optical rotation:	$[\alpha]_D^{20}$ = -21.7° (c = 1.03, CHCl$_3$)	
HPLC	major enantiomer	19.52 min
	minor enantiomer	9.90 min

(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.5 mL/min)

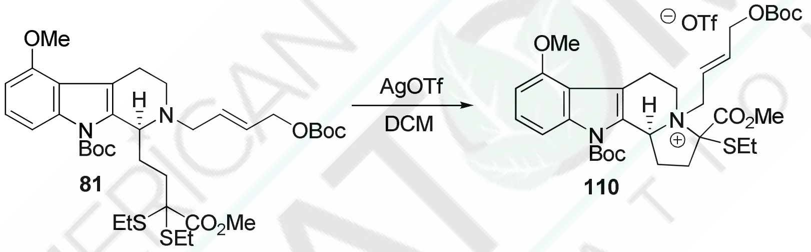
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, 1H, J=8.4Hz), 7.15 (t, 1H, J=8.2Hz), 6.65 (d, 1H, J=8.0Hz), 5.90 (m, 1H), 5.73 (m, 1H), 4.58 (d, 2H, J=6.3Hz), 4.15 (dd, 1H, J=2.3Hz, J=10.6Hz), 3.89 (s, 3H), 3.76 (s, 3H), 3.32 (dd, 1H, J=6.5Hz, J=13.7Hz), 3.22 (dd, 1H, J=6.5Hz, J=13.9Hz), 3.14 (m, 1H), 2.94 (m, 2H), 2.80 (dd, 1H, J=4.7Hz, J=16.4Hz), 2.69 (m, 4H), 2.42 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H), 1.80 (m, 1H), 1.68 (s, 9H), 1.51 (s, 9H), 1.24 (t, 6H, J=7.5Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 171.2, 153.9, 153.3, 150.2, 137.6, 134.5, 134.4, 125.8, 124.1, 118.8, 114.0, 108.8, 103.3, 83.5, 81.9, 67.0, 65.3, 57.3, 55.2, 54.8, 52.7, 41.4, 33.2, 30.0, 28.1, 27.7, 23.8, 23.7, 19.1, 13.4, 13.3 ppm.

IR: ν = 2974, 2933, 1726, 1438, 1394, 1369, 1325 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{35}H_{53}N_2O_8S_2$: 693.3199; found: 693.3248.

Deprotection of thioacetal 81 to salt 110



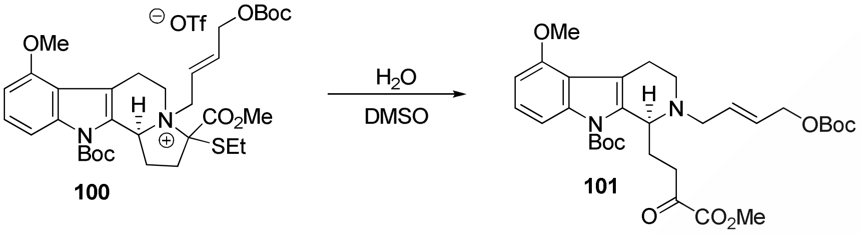
0.5623 g (0.811 mmol) 1,2,3,4-tetrahydro-*β*-carboline was dissolved in 9 mL anhydrous DCM. 0.334 g (1.3 mmol) silver trifluoromethanesulfonate was added in two portions, one at the beginning of the reaction and the second after 60 min of stirring. After 20 h of stirring at room temperature the precipitated AgSEt was removed by filtration over celite and the solvent was evaporated. The pyrrolidinium salt (as a mixture of diastereomers) was obtained as a brown foam in quantitative yield. The salt was hydrolyzed in the next step.

Yield: >99 %

^{1}H-NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.57 (d, 1H, J=8.5Hz), 7.25 (t, 1H, J=8.3Hz), 6.68 (d, 1H, J=8.0Hz), 6.20 (m, 1H), 5.94 (dt, 1H, J=5.3Hz, J=15.5Hz), 5.35 (t, 1H, J=9.0Hz), 4.58 (d, 2H, J=5.2Hz), 4.26 (dd, 1H, J=6.2Hz, J=12.4Hz), 4.05 (d, 2H, J=7.3Hz), 4.00 (s, 3H), 3.89 (s, 3H), 3.82 (m, 1H), 3.72 (dd, 1H, J=5.1Hz, J=18.8Hz), 3.12 (m, 5H), 2.84 (m, 1H), 2.40 (m, 1H), 1.68 (s, 9H), 1.48 (s, 9H), 1.30 (t, 3H, J=7.4Hz) ppm.

IR: ν = 1733 cm^{-1}.

Hydrolysis of salt 100



0.633 g (0.81 mmol) pyrrolidinium salt was dissolved in 10 mL DMSO and 2.4 mL H_2O was added. A stream of nitrogen gas was directed through the solution and it was stirred for 45 min at 75°C. The reaction was quenched with water (100 mL) and aqueous $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc. The organic layers were washed with water, the solvents evaporated and the residue purified by flash chromatography (EtOAc:PE, 1:5/1:4.5/1:4).

Yield:	73% (0.347 g, 0.59 mmol)
ee:	89%
Optical rotation:	$[\alpha]_D^{20}$ = -41.9° (c = 0.95, $CHCl_3$)

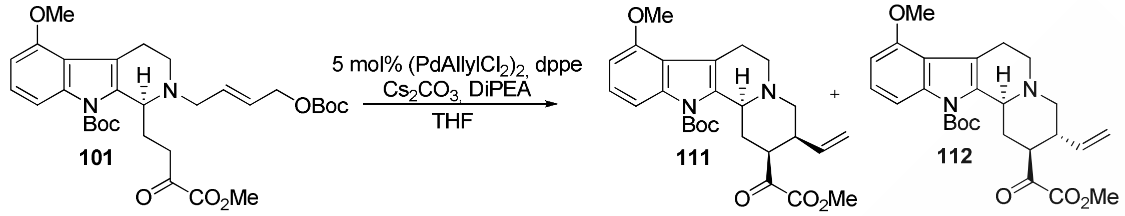
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, 1H, J=8.4Hz), 7.18 (t, 1H, J=8.2Hz), 6.66 (d, 1H, J=8.0Hz), 5.80 (m, 1H), 5.68 (m, 1H), 4.53 (m, 2H), 4.04 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.20 (dd, 1H, J=7.9Hz, J=13.4Hz), 3.07 (m, 2H), 2.81 (m, 3H), 2.58 (m, 2H), 2.29 (m, 2H), 1.69 (s, 9H), 1.51 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 188.9, 161.6, 153.8, 153.0, 149.9 137.0, 132.6, 131.5, 127.0, 124.4, 118.4, 113.9, 108.7, 103.2, 83.6, 66.5, 58.1, 55.1, 54.2, 52.3, 38.8, 36.3, 32.5, 28.0, 27.5, 18.8 ppm.

IR: ν = 2977, 1726, 1576, 1495, 1438, 1394, 1369, 1321 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{31}H_{43}N_2O_9$: 587.2924; found: 587.2972.

Tsuji-Trost cyclization to 111 and 112



0.017 g (0.042 mmol) bis(diphenyphosphino)ethane was added to a solution of 0.007 g (0.02 mmol) allylpalladium(II) chloride dimer in 2 mL of anhydrous THF under argon. The solution was stirred for 15 min before it was added to a solution of 0.233 g (0.396 mmol) α-keto-ester **101** in 5 mL of dry THF followed by 0.258 g (0.793 mmol) Cs_2CO_3 and 0.135 mL (0.793 mmol) DiPEA. The reaction mixture was stirred for 20 h at room temperature before it was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtrated and the solvent removed. Purification was finalized by column chromatography using EtOAc:PE, 3:1/2:1. The products were obtained in a ratio of *cis*:*trans* = 4 : 1 and an overall yield of 78%.

cis-isomer:

yield:	62% (0.114 g, 0.245 mmol)
ee:	89%
optical rotation:	$[\alpha]_D^{20}$ = -145.8° (c = 1.07, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, 1H, J=8.4Hz), 7.15 (t, 1H, J=8.2Hz), 6.63 (d, 1H, J=8.0Hz), 6.10 (td, 1H, J=9.9Hz, J=17.2Hz), 4.99 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.56 (dt, 1H, J=3.7Hz, J=12.4Hz), 3.03 (m, 5H), 2.88 (m, 2H), 2.67 (m, 1H), 2.25 (d, 1H, J=13.3Hz), 1.77 (dd, 1H, J=12.7Hz, J=23.8Hz), 1.63 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 194.7, 161.4, 154.0, 150.5, 138.2, 137.6, 134.3, 124.5, 118.7, 117.2, 116.6, 108.5, 103.5, 83.7, 60.9, 59.8, 55.3, 52.7, 50.9, 49.5, 40.8, 28.2, 27.0, 25.1 ppm.

IR: ν = 2978, 2942, 2800, 1724, 1606, 1579, 1495, 1439, 1405, 1394, 1369, 1358, 1323 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{26}H_{33}N_2O_6$: 469.2294; found: 469.2340.

trans-isomer:

yield:	16% (0.029 g, 0.063 mmol)
ee:	89%
optical rotation:	$[\alpha]_D^{20}$ = -38.9° (c = 0.86, $CHCl_3$)

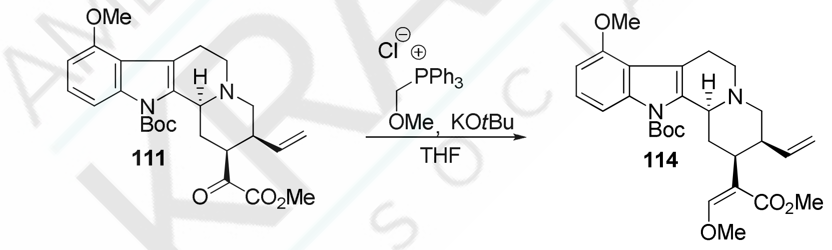
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, 1H, J=8.3Hz), 7.15 (t, 1H, J=8.2Hz), 6.63 (d, 1H, J=7.9Hz), 5.60 (m, 1H), 5.06 (m, 2H), 4.30 (d, 1H, J=10.6Hz), 3.87 (s, 3H), 3.84 (s, 3H), 3.49 (m, 1H), 3.12 (m, 3H), 2.87 (m, 5H), 2.27 (ddd, 1H, J=2.5Hz, J=3.5Hz, J=12.8Hz), 1.68 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 194.7, 161.5, 153.9, 150.1, 137.8, 137.5, 133.7, 124.3, 118.5, 116.9, 115.8, 108.6, 103.4, 83.8, 83.5, 60.2, 59.5, 57.0, 55.2, 52.7, 49.3, 46.3, 37.6, 28.6, 28.0, 24.5 ppm.

IR: ν = 2977, 2940, 2837, 1726, 1606, 1579, 1496, 1440, 1407, 1394, 1369, 1318 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{26}H_{32}N_2O_6$: 469.2294, found: 469.2340.

Wittig reaction with *cis*-isomer 111



2.6 mL of a 1M solution of KO*t*Bu in THF was added to a solution of 0.89 g (2.59 mmol) (methoxymethyl)triphenylphosphonium chloride in 6 mL THF at room temperature. The solution was cooled to -78°C and stirred for 15 min before it was added to a solution of 0.405 g (0.864 mmol) keton **111** in 10 mL THF at -78°C. The cooling bath was removed and after 1 hour of stirring at room temperature, the reaction mixture was quenched with NH_4Cl (5 mL) and EtOAc (5 mL). After stirring the quenched mixture vigorously for 12 h the mixture was extracted with EtOAc (3x), the combined organic layers were dried over Na_2SO_4. Removal of the solvent and purification by column chromatography (EtOAc:PE, 1:3, 1:2) furnished the *Z*-isomer as a brown solid.

Yield:	98% (0.419 g, 0.84 mmol)

^{1}H-NMR (400 MHz, CDCl$_3$) δ = 7.73 (d, 1H, J=8.4Hz), 7.18 (t, 1H, J=8.2Hz), 6.66 (d, 1H, J=8.0Hz), 6.075 (s, 1H), 6.05 (m, 1H), 5.07 (dd, 1H, J=2.1Hz, J=10.4Hz), 4.95 (dd, 1H, J=1.8Hz, J=17.3Hz), 3.89 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.02 (m, 4H), 2.88 (m, 2H), 2.65 (m, 2H), 2.00 (d, 1H, J=12.0Hz), 1.64 (s, 9H), 1.50 (m, 1H) ppm.

^{13}C-NMR (100 MHz, CDCl$_3$) δ = 166.8, 156.9, 153.9, 150.4, 138.4, 138.2, 134.4, 124.5, 118.6, 117.0, 116.6, 110.4, 108.2, 103.5, 83.7, 61.9, 61.6, 60.8, 55.3, 51.2, 50.8, 42.6, 39.2, 31.8, 28.1, 25.2 ppm.

IR: ν = 2944, 2838, 2798, 2751, 1727, 1692, 1645, 1579, 1495, 1438, 1360, 1328 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 497.2607; found: 497.2649.

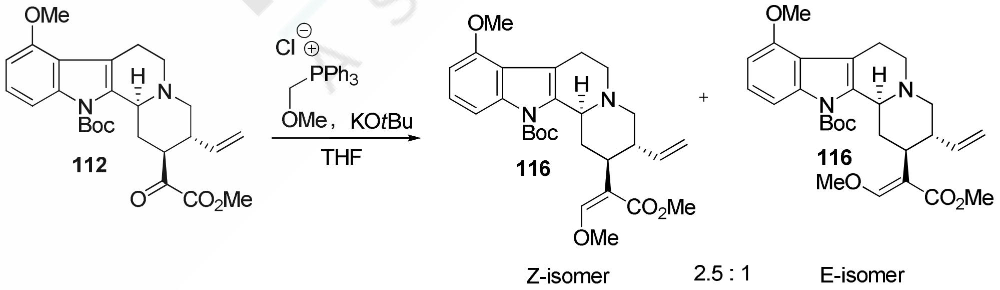
Crystallization:

The product was dissolved in a minimal amount of ethyl acetate and diluted with petroleum ether. After standing for 24 h at room temperature the crystals were removed by filtration.

Crystals: 4% *ee*, 0.0485 g, MP: 151-155°C; Filtrate: 98% *ee*, 0.371 g, 86% yield from **111**.

optical rotation:	$[\alpha]_D^{20}$ = -179.9° (c = 0.97, CHCl$_3$)	
HPLC	major enantiomer	15.22 min
	minor enantiomer	12.73 min
	(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.6 mL/min)	

Wittig reaction with *trans*-isomer 112



The reaction was performed as described for **114** using 0.109 g (0.233 mmol) of ketone **112** and three equivalents of phosphonium ylid. Purification through column chromatography gave both the *Z*-and *E*-isomer in a ratio of 2.5 : 1.

Z-isomer:

Yield: 57% (0.064 g, 0.13 mmol)
ee: 89%
optical rotation: $[\alpha]_D^{20}$ = +2.8° (c = 0.5, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, 1H, J=8.2Hz), 7.13 (t, 1H, J=8.2Hz), 6.62 (d, 1H, J=7.9Hz), 6.37 (s, 1H), 5.54 (m, 1H), 5.02 (m, 2H), 4.14 (d, 1H, J=10.20 Hz), 3.86 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.14 (m, 3H), 2.97 (m, 1H), 2.77 (m, 2H), 2.64 (dq, 1H, J=3.8Hz, J=11.4Hz), 2.44 (td, 1H, J=3.6Hz, J=12.0Hz), 2.11 (ddd, 1H, J=2.6Hz, J=3.4Hz, J=12.9Hz), 1.73 (m, 1H), 1.65 (s, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.8, 157.1, 154.0, 150.2, 139.2, 138.0, 134.6, 124.4, 118.7, 116.1, 115.4, 110.7, 108.6, 103.5, 83.6, 61.9, 60.8, 60.3, 58.6, 55.3, 51.1, 47.0, 42.4, 42.2, 34.5, 28.1, 24.6, 14.1 ppm.
IR: ν = 2937, 1724, 1320 cm^{-1}.
HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{28}H_{37}O_6N_2$: 497.2607; found: 497.2652.

E-isomer:

Yield: 21% (0.024 g, 0.047 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, 1H, J=8.4Hz), 7.28 (s, 1H), 7.13 (t, 1H, J=8.2Hz), 6.62 (d, 1H, J=8.0Hz), 5.53 (m, 1H), 4.96 (m, 2H), 4.20 (d, 1H, J=10.9Hz), 3.87 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 3.25 (m, 1H), 3.05 (m, 4H), 2.80 (m, 3H), 2.12 (q, 1H, J=12.4Hz), 1.84 (d, 1H, J=12.8Hz), 1.64 (s, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 159.4, 154.0, 150.2, 139.9, 138.1, 134.7, 124.4, 118.7, 115.3, 115.1, 112.2, 108.6, 103.5, 83.6, 61.3, 60.9, 58.1, 55.4, 51.0, 46.3, 38.5, 30.8, 28.0, 24.6 ppm.
IR: ν = 1726, 1703, 1637, 1438, 1359, 1327 cm^{-1}.
HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{28}H_{37}O_6N_2$: 497.2607; found: 497.2652.

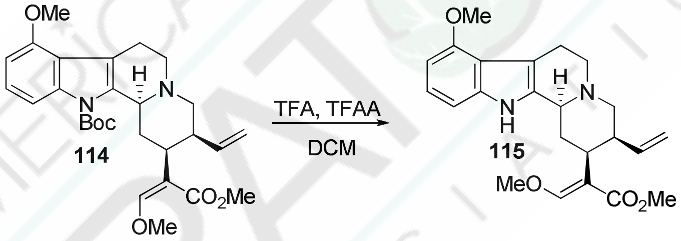
Crystallization of **116**:
116 was dissolved in a minimal amount of ethyl acetate and diluted with petroleum ether. After standing for 24 h at room temperature the crystals were removed by filtration.
Crystals: 73% *ee*, 0.0109 g, MP: 184-187°C; filtrate: 97% *ee*, 0.0051 g.

The filtrate resulting from the first crystallization was evaporated and the remaining grass dissolved and the crystallization procedure repeated.

Crystals: 99% *ee*, 0.005 g, MP: 183-187°C; filtrate: 0.0001 g.

optical rotation:	$[\alpha]_D^{20}$= +53.7° (c = 1.08, $CHCl_3$)	
HPLC	major enantiomer	18.69 min
	minor enantiomer	16.39 min
	(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.6 mL/min)	

Synthesis of (-)-dehydro-mitragynine 115



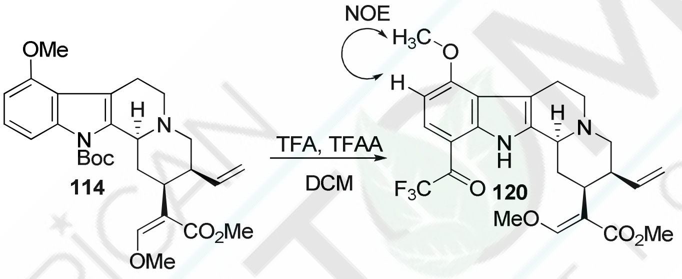
0.4 equiv. trifluoroacetic anhydride was added to 5 mL good quality TFA under anhydrous conditions. The acid-solution was given to a solution of enolether (0.0336 g, 0.068 mmol) **114** in 15 mL DCM under argon. The reaction was stirred for 17 h at room temperature before it was quenched with Et_2O and neutralized with aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O, the organic layers combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2/1:1 gave the product as a yellow solid.

Yield:	61% (0.0164 g, 0.041 mmol)
MP:	84-87°C
Optical rotation:	$[\alpha]_D^{20}$= -104° (c = 0.93, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.70 (bs, 1H), 7.35 (s, 1H), 7.00 (t, 1H, J=7.9Hz), 6.90 (d, 1H, J=8.0Hz), 6.46 (d, 1H, J=7.7Hz), 6.32 (dt, 1H, J=9.9Hz, J=17.1Hz), 4.91 (m, 2H), 3.88 (s,

3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.23 (bd, 1H, J=11.2Hz), 3.07 (m, 2H), 2.94 (m, 3H), 2.72 (dd, 1H, J=2.9Hz, J=11.2Hz), 2.55 (m, 2H), 2.42 (bd, 1H, J=7.6Hz), 1.86 (bd, 1H, J=12.8Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 169.0, 160.2, 154.4, 139.4, 137.1, 133.3, 121.8, 117.4, 114.2, 111.0, 107.8, 104.1, 99.6, 61.4, 61.2, 60.9, 60.3, 55.2, 53.5, 51.1, 44.5, 39.0, 30.2, 23.7 ppm.
IR: ν = 3364, 2936, 2838, 2791, 2752, 1698, 1643, 1597, 1570, 1507, 1460, 1435, 1350, 1309, cm^{-1}.
HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 397.2083; found: 397.2122.

Friedel-Crafts acylation of 114



1.3 mL TFAA was added to 13 mL TFA under anhydrous conditions. The TFA/TFAA-solution was given to a solution of enol ether (0.665 g, 1.339 mmol) **114** in 40 mL DCM and stirred for 20 h at room temperature. The reaction was quenched with Et_2O and neutralized with $NaHCO_3$ under strong stirring. The aqueous layer was extracted with Et_2O (3x), the organic layers combined and dried over Na_2SO_4. Column chromatography using EtOAc:PE 1:2/1:1 furnished product **120** as an orange foam.

Yield:	74% (0.489 g, 0.99 mmol)
Optical rotation:	$[\alpha]_D^{20}$= -187.6° (c = 1.18, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1H), 7.84 (m, 1H), 7.39 (s, 1H), 6.59 (d, 1H, J=8.8Hz), 6.32 (dt, 1H, J=10.0Hz, J=17.0Hz), 4.95 (m, 2H), 4.02 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.28 (d, 1H, J=11.1Hz), 3.12 (m, 2H), 2.97 (m, 3H), 2.76 (dd, 1H, J=3.1Hz, J=11.2Hz), 2.57 (m, 2H), 2.47 (dd, 1H, J=2.8Hz, J=6.5Hz), 1.99 (dt, 1H, J=2.4Hz, J=12.9Hz) ppm.

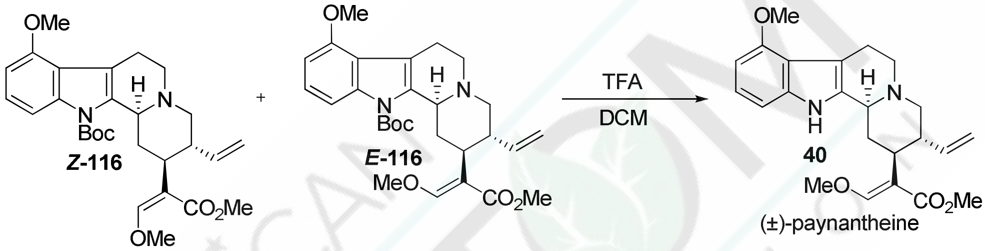
^{13}C-NMR (100 MHz, $CDCl_3$): 168.8, 161.4, 160.2, 139.2, 137.8, 135.1, 128.9, 128.9, 118.5, 117.6, 115.7, 114.4, 110.6, 108.7, 107.8, 100.7, 61.3, 61.2, 60.7, 55.6, 53.1, 51.1, 44.3, 38.9, 30.0, 23.4 ppm.

IR: ν = 2940, 2846, 2791, 2747, 1700, 1646, 1600, 1561, 1510, 1461, 1436, 1391, 1363, 1310 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{25}H_{28}O_5N_2F_3$: 493.1906; found: 493.1949.

Deprotection and isomerization to furnish paynantheine

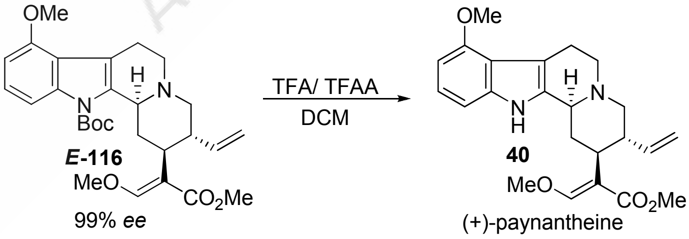
Isomerization with racemic material:



1.6 mL TFA was added to a mixture of racemic ***Z*-116** and ***E*-116** (0.162 mmol) in 4.8 mL anhydrous DCM and was stirred for 12 h at room temperature. The reaction was quenched with Et_2O and aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc, the organic layers combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2/1:1 gave (±)-paynantheine as a brown solid.

Yield: 75% (0.035 g, 0.089 mmol)

Isomerization with enantioenriched (99% *ee*) material:



1.9 µL TFAA was added to 1.7 mL TFA under anhydrous conditions. The TFA/TFAA solution was given to a solution of 0.023 g (0.048 mmol) ***E*-116** in 5.2 mL dry DCM. The solution was stirred for 17 h at room temperature. The reaction was quenched with Et_2O and aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc, the organic layers combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2/1:1 gave (+)-paynantheine as a brown solid.

Yield:	96% (0.0181 g, 0.046 mmol)
ee:	99%
optical rotation:	$[\alpha]_D^{20}$ = +20.2° (c = 0.91, $CHCl_3$)
	Lit.: $[\alpha]_D^{25}$ = +29.4° (c = 1.2, $CHCl_3$)[67]

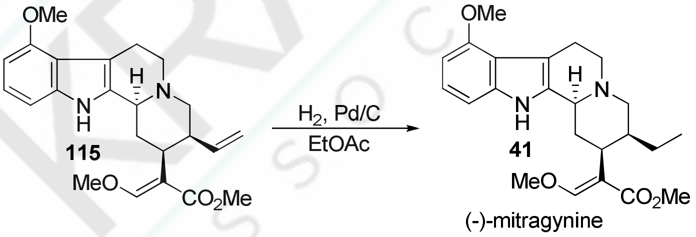
1H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (bs, 1H), 7.33 (s, 1H), 7.00 (t, 1H, J=7.9Hz), 6.87 (d, 1H, J=8.1Hz), 6.46 (d, 1H, J=7.8Hz), 5.58 (m, 1H), 4.98 (m, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 3.26 (bd, 1H, J=11.6Hz), 3.17 (m, 1H), 3.02 (m, 4H), 2.75 (td, 1H, J=3.5Hz, J=11.7Hz), 2.58 (td, 1H, J=4.2Hz, J=11.2Hz), 2.27 (t, 1H, J=11.4Hz), 2.14 (dd, 1H, J=12.0Hz, J=24.2Hz), 1.95 (d, 1H, J=12.5Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 159.8, 154.4, 139.4, 137.4, 133.0, 121.8, 117.5, 115.4, 107.8, 104.3, 99.7, 61.5, 61.3, 60.0, 55.3, 53.2, 51.3, 42.8, 33.4, 23.7 ppm.

IR: ν = 3370, 2940, 2847, 2799, 2751, 1703, 1637, 1596, 1569, 1509, 1461, 1436, 1353, 1336, 1317 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 397.2083; found: 397.2122.

Hydrogenation towards mitragynine



0.011 g (0.028 mmol) of enol ether was dissolved in 2 mL of EtOAc. 2 mg of Pd/C-catalyst was added and the suspension was stirred under H_2 atmosphere (1 atm.) for 12 h. Filtration over celite furnished (-)-mitragynine as a brown solid.

Yield:	99% (0.011 g, 0.028 mmol)
optical rotation:	$[\alpha]_D^{20}$= -112° (c = 0.66, $CHCl_3$)
	Lit.: $[\alpha]_D^{20}$ = -126 (c = 1.2, $CHCl_3$)[10]

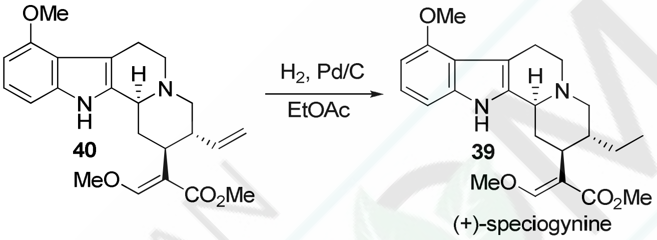
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (bs, 1H), 7.46 (s, 1H), 7.02 (t, 1H, J=7.9Hz), 6.92 (d, 1H, J=8.0Hz), 6.48 (d, 1H, J=7.7Hz), 3.90 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.13 (m, 2H), 3.05 (m, 3H), 2.94 (m, 1H), 2.53 (m, 3H), 1.79 (m, 2H), 1.66 (m, 2H), 0.89 (t, 3H, J=7.3Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ =169.2, 160.5, 154.5, 137.2, 133.7, 121.8, 117.6, 111.5, 107.8, 104.2, 99.7, 61.5, 61.2, 57.7, 55.3, 53.8, 51.3, 40.7, 39.9, 29.9, 23.9, 19.1, 12.8 ppm.

IR: ν = 3367, 2933, 2849, 2796, 2747, 1703, 1643, 1624, 1597, 1569, 1508, 1461, 1435, 1373, 1350, 1310 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{30}O_4N_2$: 399.2239; found: 399.2291.

(E)-methyl-2-((2S,3R)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate



0.0342 g (0.086 mmol) of (+)-paynantheine was dissolved in 6 mL of EtOAc and 6 mg of Pd/C-catalyst was added and the suspension was stirred for 12 under H_2 atmosphere for 12 h. Filtration over celite furnished (+)-speciogynine as a brown solid.

Yield:	99%
optical rotation:	$[\alpha]_D^{20}$ = +22.8 (c = 0.89, $CHCl_3$)
	Lit.: $[\alpha]_D^{24}$ = +26.8°(c = 0.85, $CHCl_3$)[67]

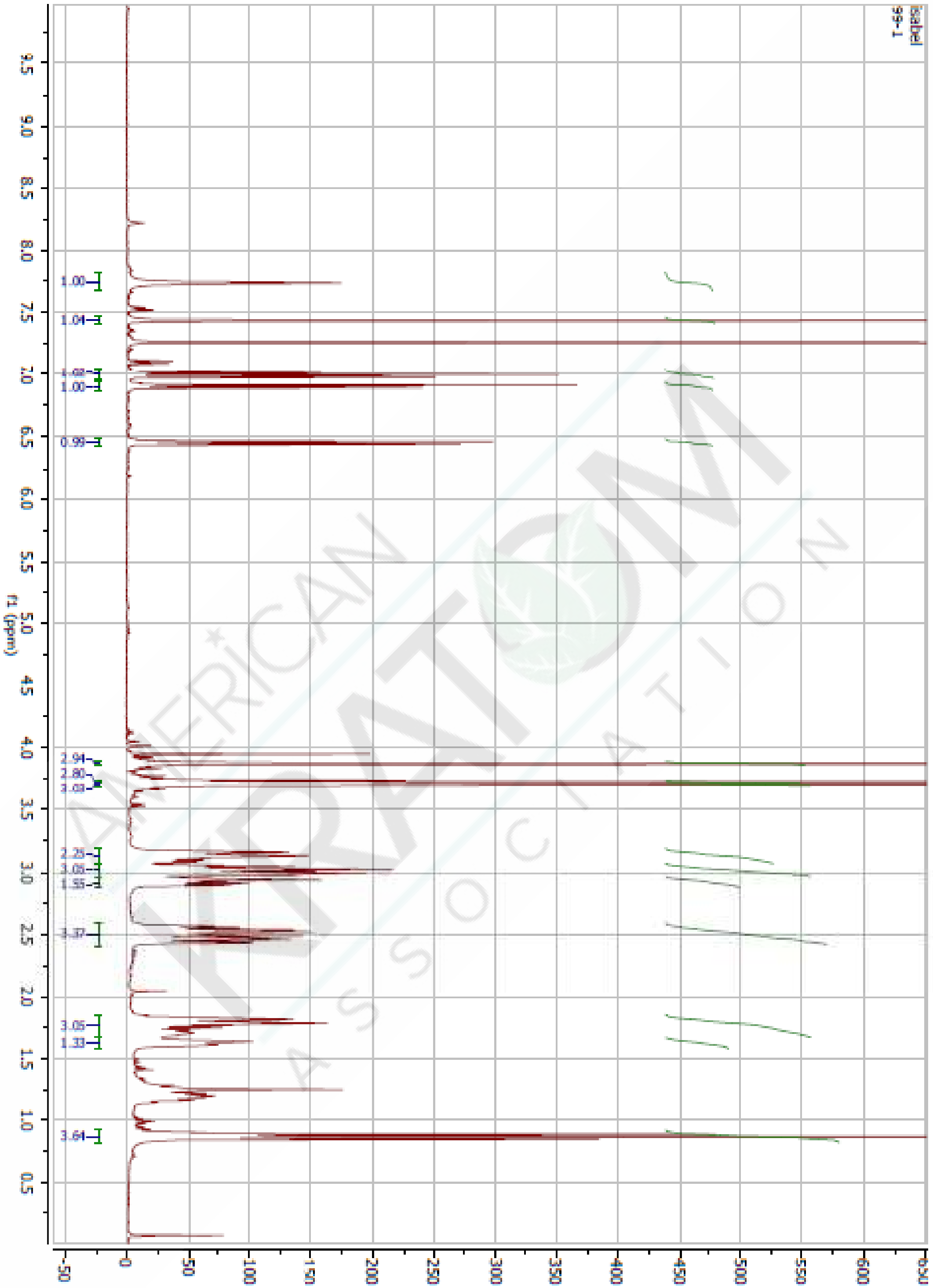
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 (bs, 1H), 7.36 (bs, 1H), 6.99 (t, 1H, J=7.9Hz), 6.86 (d, 1H, J=8.1Hz), 6.45 (d, 1H, J=7.7Hz), 3.87 (s, 3H), 3.58-3.81 (bs, 6H), 3.28-2.93 (m, 5H), 2.78-2.5 (m, 2H), 2.35-2.20 (m, 1H), 2.15-1.82 (m, 3H), 1.50-1.36 (m, 1H), 1.12-0.97 (m, 1H), 0.87 (t, 3H, J=7.4Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 159.9, 154.4, 137.4, 133.1, 121.8, 117.5, 107.7, 104.3, 99.7, 61.7, 60.9, 60.3, 55.3, 53.5, 51.5, 39.9, 38.7, 33.7, 30.6, 29.7, 24.4, 23.7, 11.3 ppm.

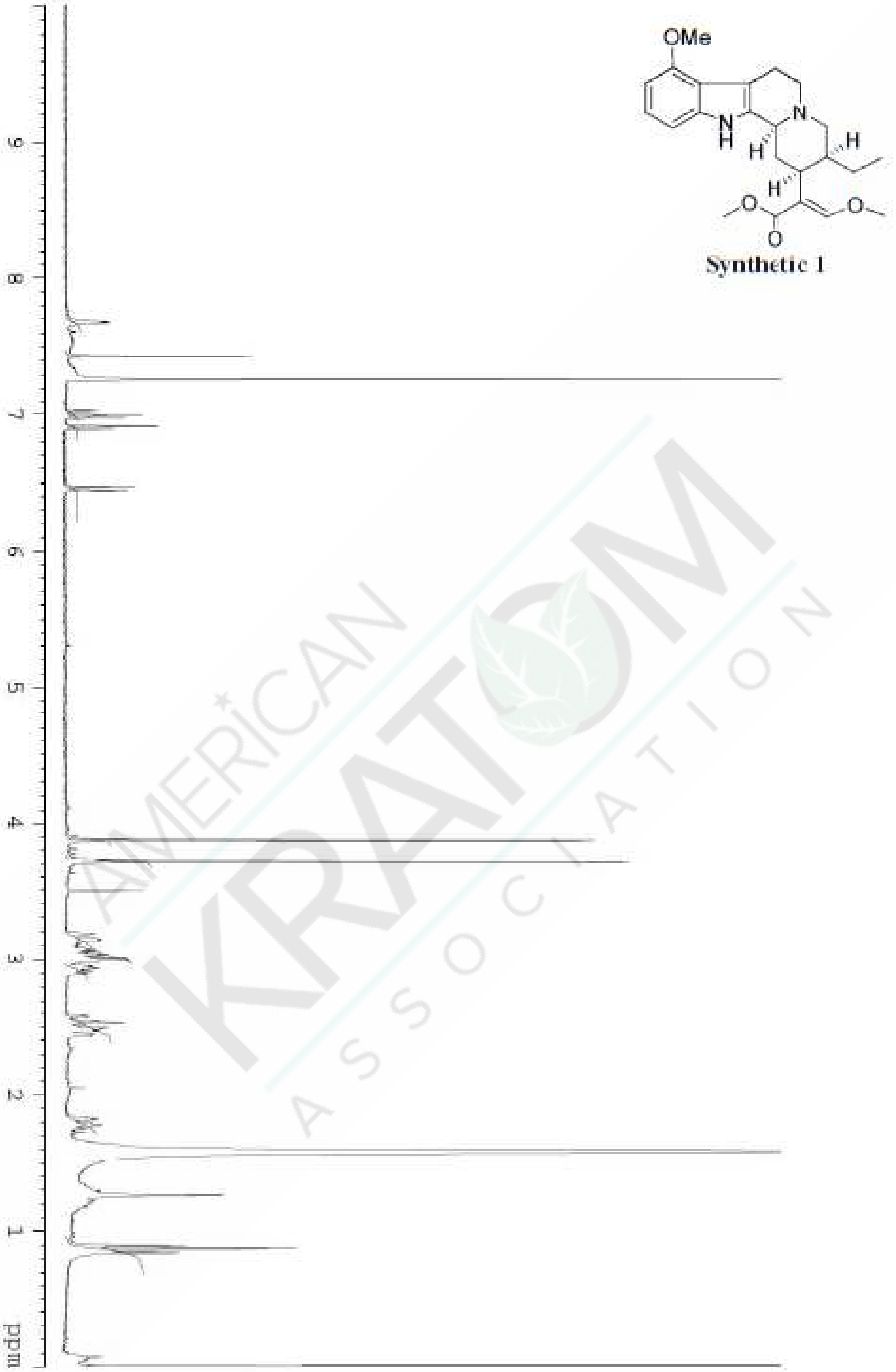
IR: ν = 2936, 2851, 2802, 2750, 1698, 1635, 1597, 1569, 1509, 1461, 1435, 1356, 1336, 1320, cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{31}O_4N_2$: 399.2239; found: 399.2289.

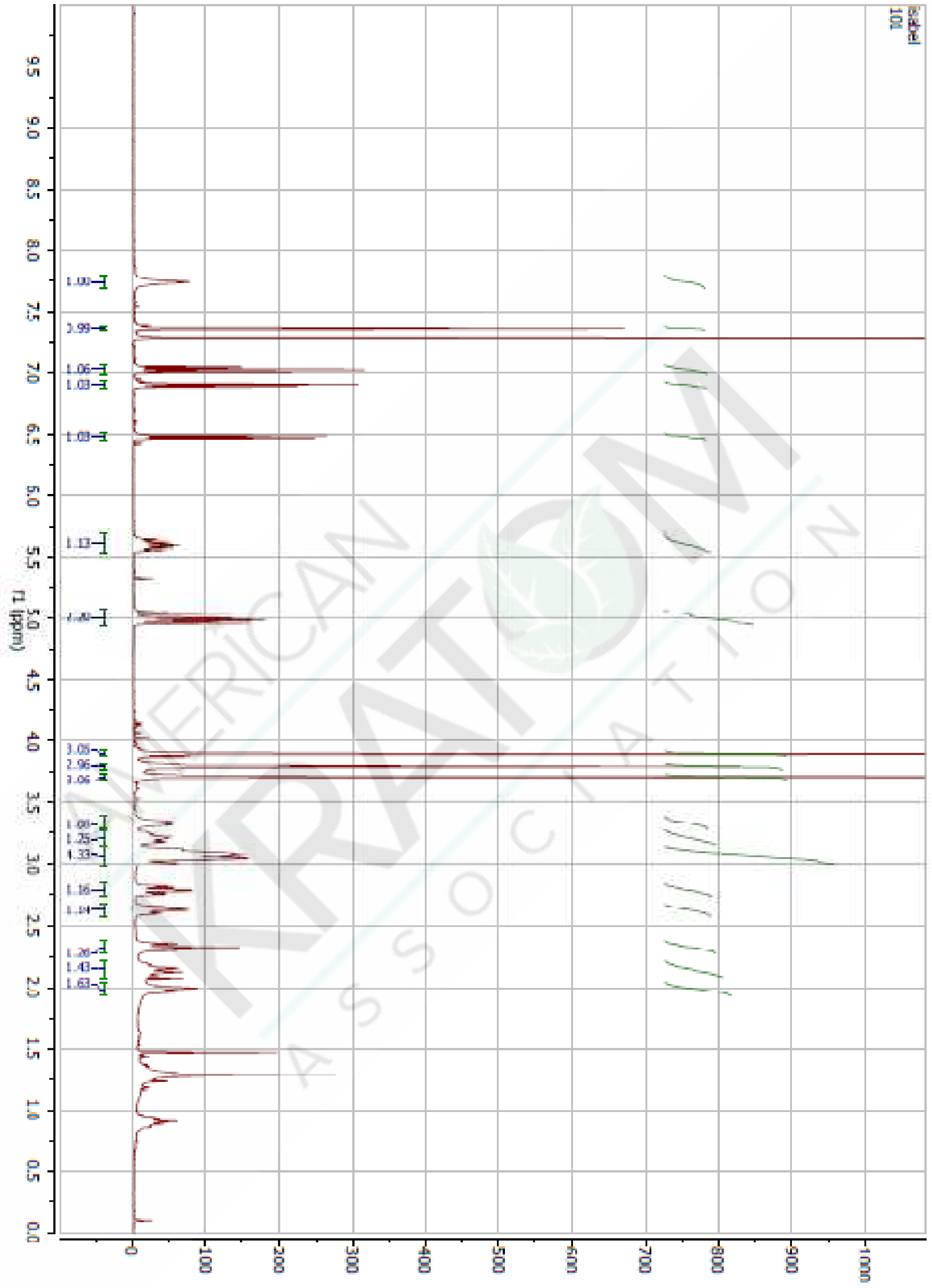
Recorded spectrum of (-)-mitragynine ($CDCl_3$, 400 MHz):



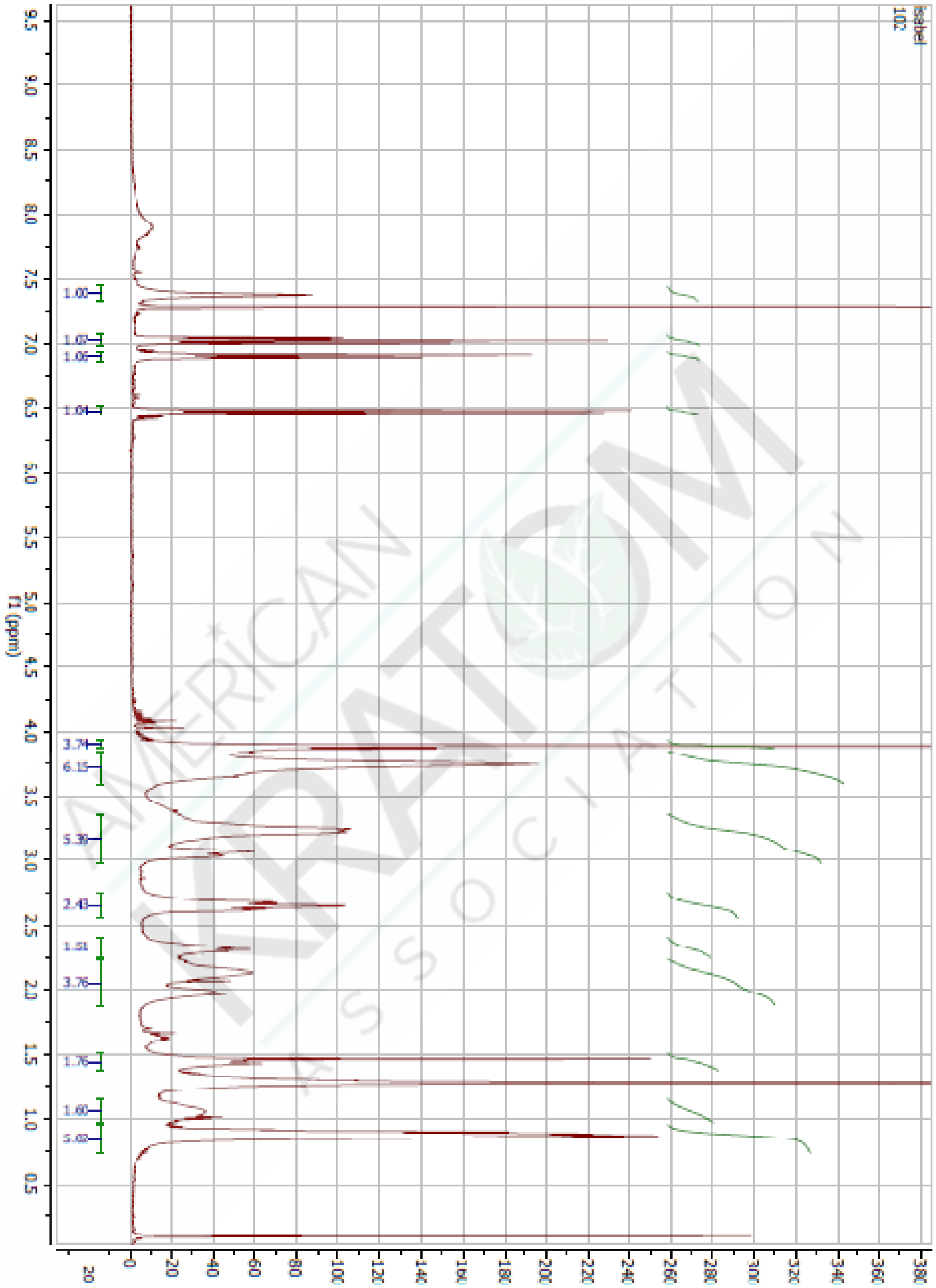
Copy of ^{1}H-NMR spectrum ($CDCl_3$, 300MHz) of (-)-mitragynine published by Cook et al.[8]



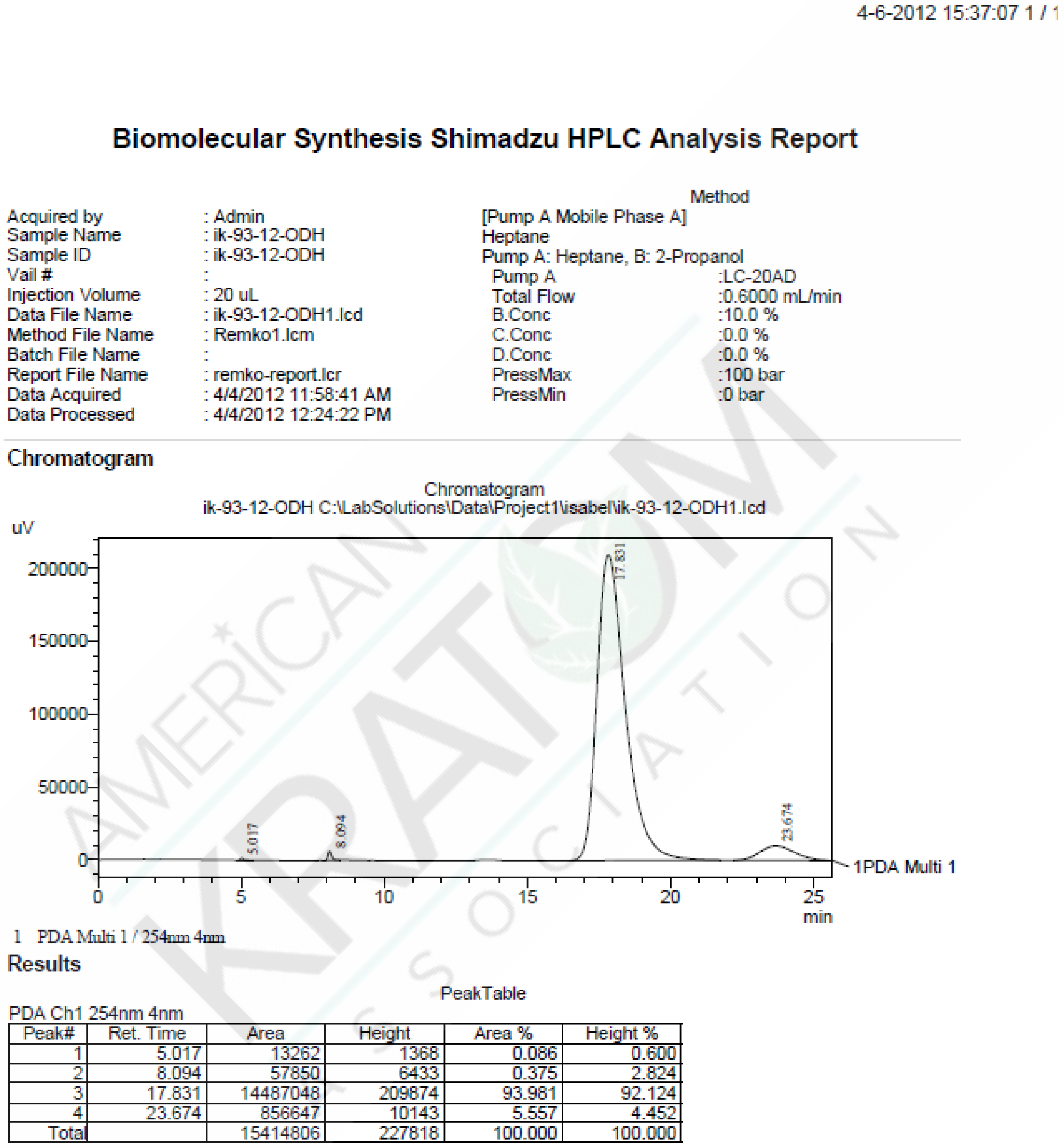
Recorded spectrum of (+)-paynantheine ($CDCl_3$, 400 MHz):



Recorded spectrum of (+)-speciogynine ($CDCl_3$, 400 MHz):



Chiral HPLC chromatogram of the Pictet-Spengler product **46** in the scale-up



4-6-2012 15:37:07 1 / 1

Biomolecular Synthesis Shimadzu HPLC Analysis Report

Acquired by : Admin
Sample Name : ik-93-12-ODH
Sample ID : ik-93-12-ODH
Vail # :
Injection Volume : 20 uL
Data File Name : ik-93-12-ODH1.lcd
Method File Name : Remko1.lcm
Batch File Name :
Report File Name : remko-report.lcr
Data Acquired : 4/4/2012 11:58:41 AM
Data Processed : 4/4/2012 12:24:22 PM

Method
[Pump A Mobile Phase A]
Heptane
Pump A: Heptane, B: 2-Propanol
Pump A :LC-20AD
Total Flow :0.6000 mL/min
B.Conc :10.0 %
C.Conc :0.0 %
D.Conc :0.0 %
PressMax :100 bar
PressMin :0 bar

Chromatogram

Chromatogram
ik-93-12-ODH C:\LabSolutions\Data\Project1\isabel\ik-93-12-ODH1.lcd

1 PDA Multi 1 / 254nm 4nm

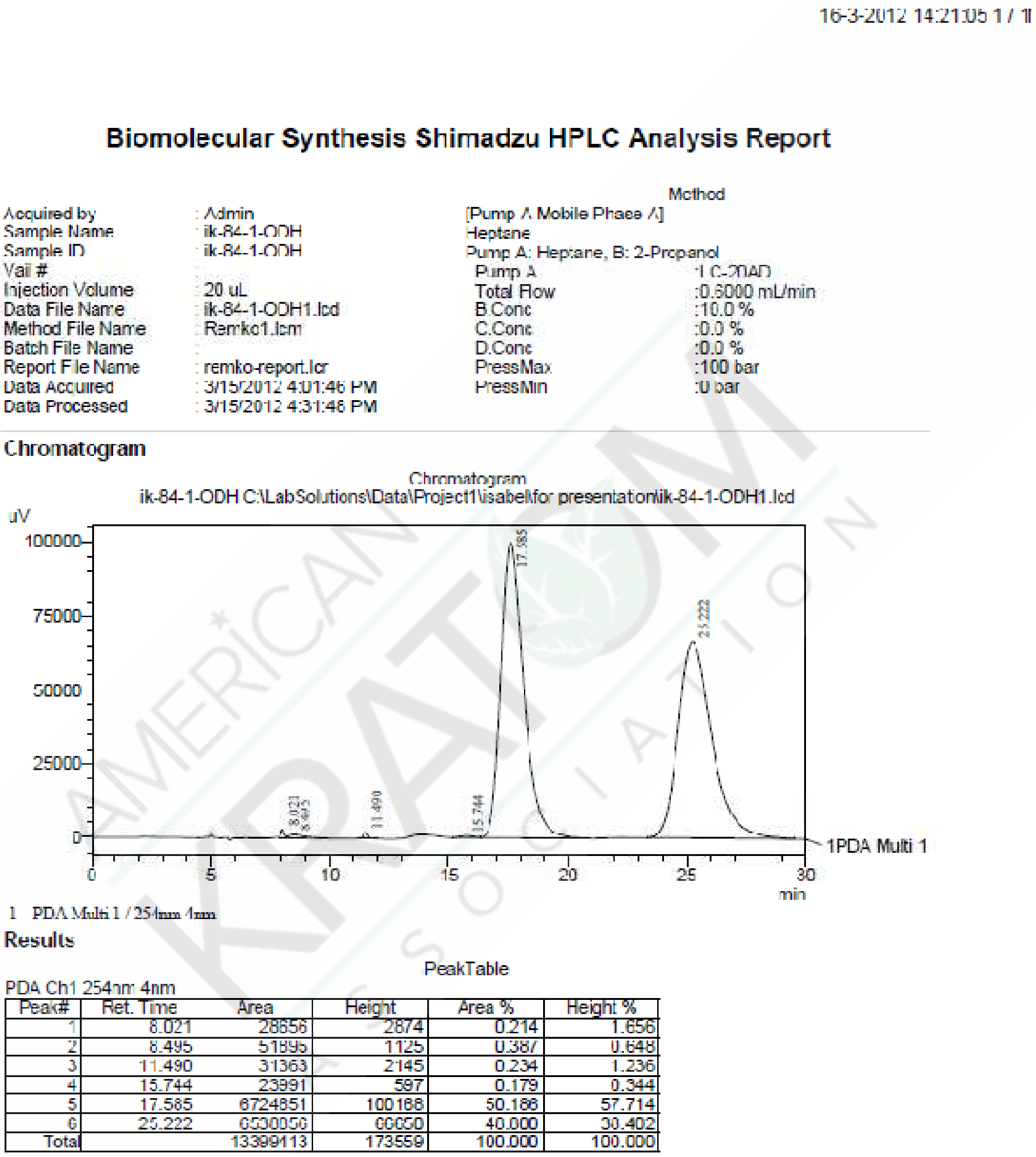
Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.017	13262	1368	0.086	0.600
2	8.094	57850	6433	0.375	2.824
3	17.831	14487048	209874	93.981	92.124
4	23.674	856647	10143	5.557	4.452
Total		15414806	227818	100.000	100.000

Chiral HPLC chromatogram of racemic **46**.



16-3-2012 14:21:05 1 / 1

Biomolecular Synthesis Shimadzu HPLC Analysis Report

Acquired by	: Admin			Method
Sample Name	: ik-84-1-ODH		[Pump A Mobile Phase A]	
Sample ID	: ik-84-1-ODH		Heptane	
Vail #	:		Pump A: Heptane, B: 2-Propanol	
Injection Volume	: 20 uL		Pump A	:LC-20AD
Data File Name	: ik-84-1-ODH1.lcd		Total Flow	:0.6000 mL/min
Method File Name	: Remko1.lcm		B.Conc	:10.0 %
Batch File Name	:		C.Conc	:0.0 %
Report File Name	: remko-report.lcr		D.Conc	:0.0 %
Data Acquired	: 3/15/2012 4:01:46 PM		PressMax	:100 bar
Data Processed	: 3/15/2012 4:31:46 PM		PressMin	:0 bar

Chromatogram

Chromatogram
ik-84-1-ODH C:\LabSolutions\Data\Project1\isabel\for presentation\ik-84-1-ODH1.lcd

1 PDA Multi 1 / 254nm 4nm

Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.021	28656	2874	0.214	1.656
2	8.495	51895	1125	0.387	0.648
3	11.490	31363	2145	0.234	1.236
4	15.744	23991	597	0.179	0.344
5	17.585	6724851	100188	50.188	57.714
6	25.222	6530056	66650	40.000	30.402
Total		13399113	173559	100.000	100.000

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Herbal Medicines for the Management of Opioid Addiction

Safe and Effective Alternatives to Conventional Pharmacotherapy?

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Abstract

Striking increases in the abuse of opioids have expanded the need for pharmacotherapeutic interventions. The obstacles that confront effective treatment of opioid addiction – shortage of treatment professionals, stigma associated with treatment and the ability to maintain abstinence – have led to increased interest in alternative treatment strategies among both treatment providers and patients alike. Herbal products for opioid addiction and withdrawal, such as kratom and specific Chinese herbal medications such as WeiniCom, can complement existing treatments. Unfortunately, herbal treatments, while offering some advantages over existing evidence-based pharmacotherapies, have poorly described pharmacokinetics, a lack of supportive data derived from well controlled clinical trials, and severe toxicity, the cause for which remains poorly defined. Herbal products, therefore, require greater additional testing in rigorous clinical trials before they can expect widespread acceptance in the management of opioid addiction.

1. Introduction

Striking increases in the abuse of opioids have been observed over the last decade in the US, Eastern Europe, China and the Middle East.[1-3] As rates of abuse and addiction have grown, the need for pharmacotherapeutic interventions has increased as well. Unfortunately, obstacles such as shortages of treatment centres and addictionologists inhibit the delivery of evidence-based pharmacotherapies such as methadone and coformulated buprenorphine/naloxone in many locations.[3,4] In addition, there are high rates of relapse associated with conventional interventions for opioid addiction. Finally, the stigma of receiving daily opioid replacement therapy in public venues such as methadone clinics may prevent some from seeking treatment in the first place.

The limitations of currently available conventional pharmacotherapies for opioid addiction may compel some individuals to use therapies that are more easily obtainable, perceived as having longer-lasting effects, and/or greater social acceptability. As a result, interest in alternative treatment strategies for opioid addiction has increased among both treatment providers and patients alike.[5,6] Formulations of the more recognized alternative interventions, kratom and ibogaine, are derived from herbal material, but a number of Asian remedies used in the management of opioid abstinence syndromes incorporate animal and mineral materials as well. This review will describe the pharmacology, toxicology and efficacy of herbal-based interventions, as well as assess potential risks to users. To identify the material synthesized in this review, we conducted initial searches of the English language literature using PubMed and Google Scholar databases. We did not restrict our search results by date. Results from these primary searches served as starting points for secondary searches related to specific topical matter for inclusion in the review. Although we relied upon peer-reviewed primary literature as sources for medical and scientific data, we cited anecdotal publications describing historical events related to clandestine treatments.

2. Kratom

Kratom (Mitragynia speciosa Korth) is a tree found in Southeast Asia that contains medicinally relevant alkaloids known as mitragynines within its leaves.[7-9] The ability of the plant to produce these compounds is highly dependent on geography; plants growing in Southeast Asia elaborate mitragynines, but those grown elsewhere, even in tropical greenhouses, do not. Kratom leaves have traditionally been used as a substitute for opium or to treat withdrawal, as well as for their stimulant effects.[10] Moreover, Thai villagers use extracts of kratom leaves as a medicine to treat cough, diarrhoea and musculoskeletal pain.[8,10] Ingestion by chewing, smoking, brewing into a tea, or swallowing a tarlike solid that has been extracted and reduced from the leaves are typical modes of administration.[7]

The predominant alkaloid isolated from kratom extracts is mitragynine; a minor component is 7-hydroxymitragynine, an oxidized congener.[8] These compounds appear to be responsible for the analgesic effects of kratom through opioid receptor binding *in vivo* and *in vitro*.[11] Animal studies have demonstrated that the antinociceptive activity of mitragynine in the tail-pinch and hotplate tests is completed abolished by the pure opioid receptor antagonist naloxone.[12] Repetitive administration of 7-hydroxymitragynine produces tachyphylaxis as well as cross-tolerance to morphine.[10] Furthermore, administration of naloxone to 7-hydroxymitragynine- and morphine-dependent rats produces abstinence symptoms of comparable intensity.[13] Moreover, the chemical structure of the mitragynines also incorporates the tryptamine nucleus, which may be responsible for the observed activity of the molecules in the serotonin and adrenergic systems.[8] The mitragynines, however, have a novel structural scaffold for opioid receptor affinity and activity.[8,14] For example, both molecules contain the amino functionality and the phenolic moiety common to all opioid-based ligands.[8,15] Interestingly, based on the current understanding of the structure-activity relationships for the mitragynines, the phenolic methyl ether is more potent in analgesic paradigms.[11] This is in contrast to morphine where methylation of the phenol moieties (to produce codeine) reduces analgesic potency; for morphinan-based ligands, the phenolic hydrogen provides critical interactivity with the opioid receptors.[16]

The pharmacokinetics of kratom in humans are poorly described; for example, the volume of distribution, half-life, protein binding, metabolism and elimination in humans are unknown. Clinical effects appear to be dose dependent.[7,17,18] In small amounts, manual labourers use kratom for its stimulant effects so that they may work in harsh conditions.[17,18] With larger doses, the euphoric effects of kratom are the basis for its use as a replacement therapy for opium among addicts.[17,18]

Clinical effects of kratom mimic those of a μ-opioid receptor agonist.[19] As early as 1897, kratom was recognized as an analgesic, antitussive, antidiarrhoeal and as a remedy for opium withdrawal. To date, however, no formal clinical trials have studied the efficacy and safety of kratom in the treatment of opioid addiction. Adverse effects from kratom are limited. Kratom use does not appear to be associated with the emesis that commonly accompanies opioid use. Interestingly, respiratory depression following kratom administration has not been observed in either humans

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or in animal toxicity studies; even in rats that received high oral doses of mitragynine (up to 807 mg/kg), respiratory depression did not occur.[20] Similarly, no evidence of respiratory depression was observed in mice at oral doses up to 920 mg/kg of mitragynine.[20] In humans, generalized tonic-clonic seizure activity has been documented in at least two cases; neither individual had a history of seizure disorder nor was taking a pro-convulsant substance.[19,21] Chronic use of kratom has been associated with anorexia, weight loss, constipation and hyperpigmentation of the face.[9] An abstinence syndrome similar to mild opioid withdrawal is characterized by rhinorrhoea, insomnia, lacrimation, lethargy, myalgias, arthralgias and myoclonus.[9] Although confined to anecdotal reports, a relatively mild rhinorrhoea has been the leading complaint of individuals suffering withdrawal following rapid cessation of kratom use.[19]

Despite a paucity of pharmacokinetic, pharmacodynamic and toxicological data, kratom appears to enjoy widespread use among specific populations.[19,22] An ethnographic study has examined website postings generated by individuals who self-treat chronic pain with opioid analgesics purchased from online pharmacies.[22] Striking increases in the number of posts generated by the study population that identified kratom as a highly effective method for treating opioid withdrawal and promoting abstinence from prescription opioid analgesics were seen over a 12-month study period.[22] In addition, case report-level data have reported the use by an individual of kratom as an effective replacement therapy for parenteral hydromorphone abuse.[19] Formal epidemiological data describing kratom use in the general population are lacking, but the number of websites that sell kratom – sometimes in kilogram quantities – suggests the popularity of the herbal product.[22]

While kratom may have medicinal uses, it also carries some abuse liability. Although unscheduled in the US, kratom has been criminalized in a number of countries around the Pacific Rim, including Australia.[7] Compulsive use of kratom in a number of distinct populations, including injection opioid abusers and individuals with chronic pain who self-prescribe opioid analgesics, is a well described phenomenon.[19,22] Moreover, reports that students at some college campuses congregate to drink decoctions of kratom at ‘tea parties’, as well as the sale of kratom in bars, suggest its recreational use may be growing.[23,24] For populations who are too young to legally ingest ethanol, kratom may be a viable option to drinking in bars and may be a precursor to problematic opioid use.[23]

3. Ibogaine

Ibogaine is an indole alkaloid hallucinogen derived from the root bark of the African shrub *Tabernanthe iboga*.[25] Among indigenous peoples, ibogaine plays an integral role in ethnoreligious ceremonies where it induces hallucinations of protracted duration.[25] The hallucinogenic effect of ibogaine eventually led to recreational use, and in the early 1960s a young heroin addict experimenting with ibogaine claimed that he felt no opioid craving after experiencing potent ibogaine-triggered hallucinations.[26] A group of self-treating heroin addicts reported the same outcome following ibogaine use, leading to a small number of uncontrolled studies among opioid and cocaine abusers that have led some investigators to attribute substantial curative powers to ibogaine.[26] Of even greater interest has been the proponents’ claim that ibogaine-mediated detoxification from opioids was associated with dramatically lower rates of relapse than conventional therapy.[26] Unfortunately, the wealth of animal data directed toward establishing the neurochemical basis of the putative anti-addiction effects of ibogaine has failed to overcome persistent concerns about the safety of the drug.[27,28] Consequently, outcomes from ibogaine-based treatment of opioid addiction are poorly defined because the drug has yet to be entered into rigorous clinical trials. At present, ibogaine carries a US Drug Enforcement Administration Schedule I classification and is deemed to have no clinical value.[28,29]

Comprehensive pharmacological data for oral administration of ibogaine are lacking. Ibogaine is a highly lipophilic molecule that is absorbed following oral, mucosal and intraperitoneal administration. Ibogaine undergoes extensive first-pass

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metabolism.[25] Demethylation by cytochrome P450 (CYP)2D6 to noribogaine occurs in the gut and liver; after absorption from the gastrointestinal tract, ibogaine distributes to tissues according to a two-compartment model. Ibogaine and noribogaine distribute to the spleen, liver, brain and lung; both drugs cross the blood-brain barrier and are secreted in bile.[30] Estimated α and β elimination half-lives of ibogaine are approximately 7.3 minutes and 3.3 hours, respectively. Drug clearance rates are calculated at 5.6 L/hours.[31]

The exact neurochemical mechanisms underlying the putative anti-addictive properties of ibogaine have not been elucidated but likely involve modulation of multiple neurotransmitter systems.[25] Ibogaine agonizes the μ- and κ-opioid receptors, although binding affinity is dependent on experimental technique; ibogaine also antagonizes glutamate NMDA, as well as α3β4 nicotinic, receptor sites.[32-39] This observation has led to the hypothesis that the anti-addictive effects of ibogaine may arise from complex intracellular signalling cascades that reset neuronal function and eliminate drug craving.[40,41] Unfortunately, this hypothesis awaits further investigation.

Although ibogaine has been used to treat the compulsive use of cocaine, methamphetamine, ethanol and other drugs, its greatest recognition is for the management of opioid addiction. Only a handful of cases describing treatment outcomes, however, have been published despite nearly 50 years of experience using ibogaine for opioid abuse.[25] Moreover, the quality of the methodology described in these publications is frequently substandard, with the studies being poorly controlled, enrolling small numbers of participants and with often short durations of evaluation.[26,42-45] One publication described the treatment of 33 patients undergoing acute opioid withdrawal with nonstandardized ibogaine doses over a 31-year period; participants were followed for up to 72 hours after ibogaine treatment, a period so short that the major reported finding, absence of drug-seeking behaviour, is almost meaningless.[43] Another study conducted by ‘a loosely-knit organization’ of an ‘Amsterdam squatter community’ described administration of nonstandardized ibogaine doses to seven patients to treat opioid withdrawal symptoms.[42] Of these individuals, three used heroin during the 24-hour treatment period or immediately thereafter; 71% of participants relapsed to opioid abuse within 3 weeks of treatment.[42] These results support the central finding of the study that ibogaine induces an interruption in heroin use, although the benefit of ibogaine is unclear if recipients relapse to heroin use during a treatment period of approximately 24 hours in length. In addition, an open-label study conducted at a private detoxification facility in the Virgin Islands involved administration of fixed doses of ibogaine to 27 cocaine- and heroin-dependent individuals who were followed for up to 1 month.[45] Unfortunately, the total number of heroin-dependent patients, the time from last use of heroin and the number of participants completing treatment was not reported in this publication.[45] These shortcomings, coupled with the observation that expensive treatments often entice patients to distort the benefits of the intervention, raise questions about the extent to which any beneficial effect was realized.[46] No controlled trials using ibogaine have been published in the peer-reviewed literature.

Because ibogaine is most commonly administered in unconventional settings, formal data on the clinical and adverse effects of the drug are lacking.[47] Clinical findings associated with ibogaine ingestion include profound vomiting for many hours, sometimes longer than 1 day. The most prominent feature of ibogaine use, open- and closed-eye hallucinations, occurs at oral doses of greater than 200–300 mg.[42] Above this dosage range, ibogaine has been associated with hallucinations that may persist for up to 36–48 hours.[42,48,49] Cerebellar dysfunction, including ataxia, tremor and nystagmus, is commonly observed and has an onset within 2–4 hours of drug administration. These signs may resolve within 12 hours of use.[49] Individuals ingesting ibogaine have also reported muscle pain and soreness that persist beyond resolution of the neuropsychiatric effects.[47]

The most feared complication of both ‘therapeutic’ and exploratory ibogaine use remains sudden death, most likely due to *torsades de pointes* arising from prolongation of the QT interval.

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One patient who survived ventricular dysrhythmias following ibogaine administration had dramatic prolongation of the QT interval to 616 msec when corrected for heart rate.[50] Two features of this patient's clinical course are notable. First, the QT interval was unresponsive to the standard intervention of rapid electrolyte correction.[50] Second, the QT interval remained prolonged for a protracted period, normalizing during the second hospital day.[50] This derangement in cardiac rhythm may not be unique to this patient. At least 11 sudden deaths have been associated with ibogaine use, but in each case, the cause of death could not be determined despite autopsy.[50,51] Despite extensive investigations using animal models into the neurochemical properties of ibogaine, little effort has been directed toward understanding the basis of its cardiotoxicity.[52]

4. Chinese Herbal Remedies

Opioid abuse and addiction have been a public health hazard in China for much of the last 200 years.[3] Governmental policies enacted in the 1950s curtailed opioid abuse, but economic reforms of the 1980s led to a widespread resurgence of heroin addiction.[3] To confront the growing problem of drug addiction, the Chinese government has initiated pharmacotherapy programmes based on Western addiction treatment protocols.[3] Unfortunately, the predominant treatment for opioid addiction is short-term detoxification with methadone or buprenorphine at compulsory reeducation-through-work centres.[3] These programmes have faced great difficulties. Treatment centres are underfunded, and because patients undergo forced detoxification, they have high rates of relapse and low rates of recovery.[3] Finally, many opioid addicts live in rural areas, where the reach of treatment programmes is limited.[3]

Traditional Chinese medicines have therefore received considerable interest as potentially more acceptable and less costly alternatives to standard pharmacotherapy. The Chinese State Food and Drug Administration has approved at least ten herbal-based products for the treatment of opioid withdrawal, with several more in clinical trials.[3] Although Asian herbal remedies are often mixtures of plant matter, animal material and, in some cases, minerals or even toxic metals, the use of specific components in these complex mixtures as treatment for opioid withdrawal is supported by preclinical and clinical data.[53,54]

Corydolis yanhusuo is a herbal analgesic with sedative, hypnotic and antihypertensive properties.[55] The active component, the natural product levotetrahydropalmatine (l-THP), inhibits in a murine model the locomotor hyperactivity induced by oxycodone.[56] In addition, treatment with l-THP can attenuate morphine-induced withdrawal syndromes and conditioned place preference in mice.[57] These promising preclinical findings have triggered clinical investigations of l-THP. In a randomized, double-blind, placebo-controlled clinical trial, l-THP was administered to 120 heroin addicts over a 4-week period.[58] Although l-THP effectively reduced opioid craving, withdrawal syndromes and relapse rates in heroin-dependent patients, several features of this trial deserve mention.[58] First, all study participants had completed a 7-day detoxification period before enrolment in the study; virtually none, therefore, were likely to have been in acute withdrawal.[58] Second, of the 59 participants randomized to the l-THP group, only 44 'survived' 2 of the 4 weeks of treatment whereas 59 of 61 participants who received placebo completed 2 of 4 weeks of treatment.[58] Third, the authors never state the number of participants in either group who completed the 4-week treatment period.[58] Less than half of the l-THP-treated individuals who remained in the study at 2 weeks remained abstinent at 3 months; any beneficial outcomes, therefore, could have been driven by increased motivation to overcome addiction in a subset of the treatment population as much as from the effect of l-THP.[58]

Ginseng is another botanical commonly used in Chinese traditional remedies.[53] Two major types of ginseng exist, *Panax ginseng* (Asian ginseng) and *Panax quinquefolium* (American ginseng). The main active natural products in *Panax ginseng* are called ginsenosides, of which more than 20 have been characterized.[59] Ginsenosides have putative effects on the CNS and cardiovascular system, and may alter metabolism and immune

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function.[60] *Panax ginseng* attenuates the physiological effects of drugs of abuse including morphine in pre-clinical studies.[61] A multicentre clinical trial found that Radix ginseng (the root of *Panax ginseng*) was safe and effective for the treatment of moderate-to-severe acute heroin withdrawal.[62] In this double-blind study, 212 heroin addicts were randomized to treatment with either the ginseng herbal mixture or to lofexidine over a 10-day period.[62] The investigators found that the herbal mixture was as effective as lofexidine at alleviating the symptoms of opioid withdrawal, with patients reporting only gradual improvement in symptomatology over the study period.[62] Unfortunately, lofexadine is minimally effective at treating acute opioid withdrawal, and the study design did not incorporate a placebo arm.[62] It is therefore possible that what was observed in the patients was untreated opioid withdrawal, the natural history of which is improvement over time. Significant adverse effects included elevations of liver transaminases, but because Chinese herbal mixtures are manufactured with little regulatory oversight, the specific cause of hepatic injury cannot be ascribed.[62,63]

The active chemical in *Panax quinquefolium,* not found in *Panax ginseng*, is pseudoginsenoside-F11 (PF11), a saponin.[59] *Panax quinquefolium*, especially PF11, exerts distinct effects following morphine administration. PF11 attenuates memory impairment in the Morris water maze test, analgesia measured by tail pinch, locomotor sensitization and, at higher doses, the expression of conditioned place preference.[64] Neurochemically, PF11 antagonizes opioid receptor signalling and decreases the concentrations of dopamine and its metabolites in the brain of test animals treated with morphine.[65,66] While these findings suggest that formulations containing PF11-elaborating herbal products can be applied to the management of opioid withdrawal, the clinical evidence supporting their use is mixed. For example, WeiniCom is a herbal product mixture that contains *Corydalis* and *Panax quinquefolium*; some formulations that are sold online appear also to contain kratom (*Mitragynia* spp.).[67] A double-blind, clinical trial compared WeiniCom (also called Xian Xu Qudu Jiaonang) treatment with buprenorphine in 42 heroin addicts entering treatment.[68] WeiniCom not only relieved opioid cravings more rapidly than buprenorphine, it also treated subjective measures of withdrawal symptoms such as abdominal pain, diarrhoea, rhinorrhoea, myalgias and piloerection.[68] Adverse effects from WeiniCom were not reported.[68] The beneficial effects from WeiniCom could have been due to kratom because (i) kratom appears to treat opioid withdrawal; (ii) some WeiniCom formulations contain kratom; and (iii) the exact composition of Chinese herbal remedies is often poorly defined.

In addition, a randomized, double-blind, placebo-controlled, multicentre study compared another Chinese herbal mixture called Tai-Kang-Ning with lofexidine in 64 heroin addicts.[69] Improvement in symptomatology by treatment day 3 was achieved in both groups. Because patients were enrolled up to 36 hours after last heroin use, however, and the symptoms of untreated, acute heroin abstinence resolve in approximately 5 days, this Chinese herbal medication may have actually had little impact on withdrawal.

Although the side-effect profile of traditional Chinese remedies is often unreported, the low incidence of adverse effects compared with lofexidine suggests that they are safe to use.[62,69,70] For example, a product known as FYP (Fu Yan Pellet) was tested against lofexidine in a randomized, double-blind, placebo-controlled, multicentre trial in 225 heroin addicts.[70] In this study, treatment with either FYP or lofexidine decreased opioid withdrawal symptoms by day 3 of treatment.[70] The incidence of adverse effects from FYP (e.g. dry mouth) was comparable to that of lofexidine (e.g. dry mouth, transient hypotension and bradycardia). Notably, respiratory depression from traditional remedies has not been reported in the peer-reviewed literature.

5. Heantos

Heantos, a complex mixture of materials created by a Vietnamese herbalist, is intended to treat opioid addiction.[71] Despite funding from the United Nations and other sources, this product has not yet been tested in formal clinical trials.[71] Furthermore, unconfirmed reports of at least six

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deaths associated with heantos therapy have led Vietnamese authorities to proscribe heantos therapy.[72,73] Some investigators suspect that the main component of heantos may be kratom.[72]

6. Conclusions

Clinicians hoping to incorporate herbal remedies into treatments for opioid withdrawal and addiction will be confronted by a striking lack of data from well constructed clinical trials investigating the efficacy and effectiveness of these substances. Nonetheless, herbal treatments for problematic opioid use offer some advantages over existing pharmaceutical-based interventions. Some, such as kratom, are believed to have less respiratory depression and fewer lethal side effects than methadone therapy; others, such as traditional Chinese remedies, are less expensive and may be more culturally relevant than standard opioid replacement protocols. To fully incorporate herbal interventions into existing treatment regimens, several lines of evidence should be developed.

First, the pharmacology, pharmacokinetics and toxicology of herbal materials in humans should be described in greater detail. For example, the pharmacological basis of kratom-associated seizure activity should be investigated, as well as the clinical features that place individuals at risk for this outcome. In addition, the impact of ibogaine administration on the QT interval and other cardiac effects should be investigated rather than discounted. Second, sufficient rigor should be incorporated into clinical research studies to allow meaningful assessments of outcome. For example, a study design that compares a remedy with an intervention does not allow clinicians to determine if that remedy is more effective than placebo. If a herbal substance has no benefit, then its use carries only risk; using proper study design would ensure that the potential for benefit can be incorporated into decisions related to medication selection. Third, clinicians should develop the social and cultural contexts in which herbal remedies have utility. For example, methadone-based opioid detoxification in some cultures has been associated with high rates of relapse and treatment failure. Studies that examine the contexts in which culturally relevant interventions may be incorporated into evidence-based treatment regimens may improve outcomes. Ultimately, herbal therapies for opioid addiction and withdrawal can complement existing treatments, and future studies should explore the relationship between evidence-based pharmacotherapies and traditional remedies.

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(54) **METHODS FOR TREATING WITHDRAWAL FROM ADDICTIVE COMPOUNDS**

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A61P 25/36 (2006.01)

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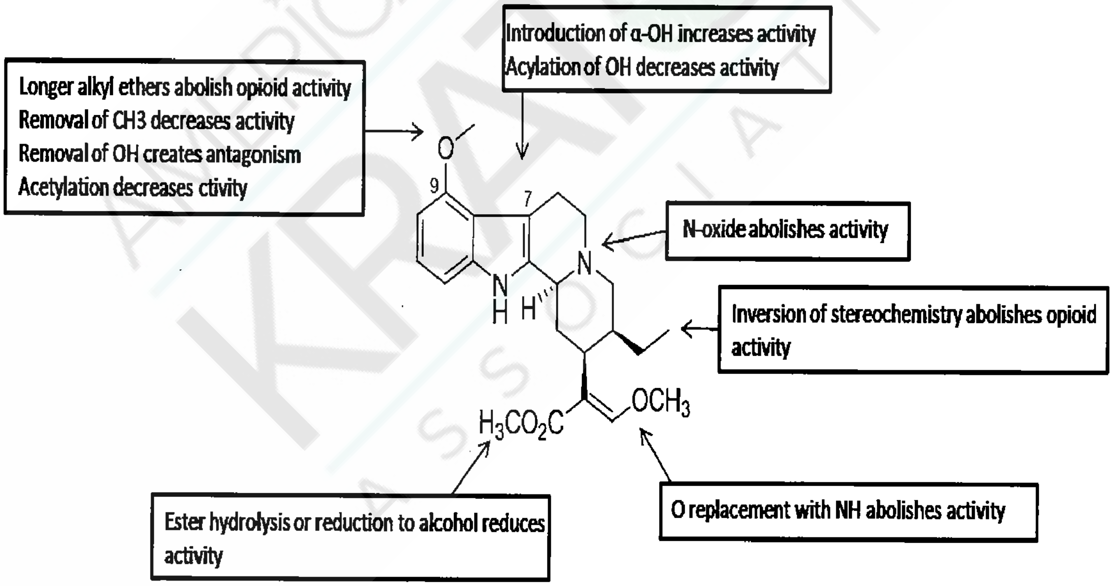
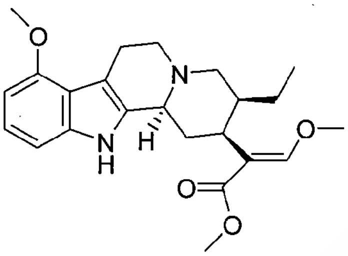
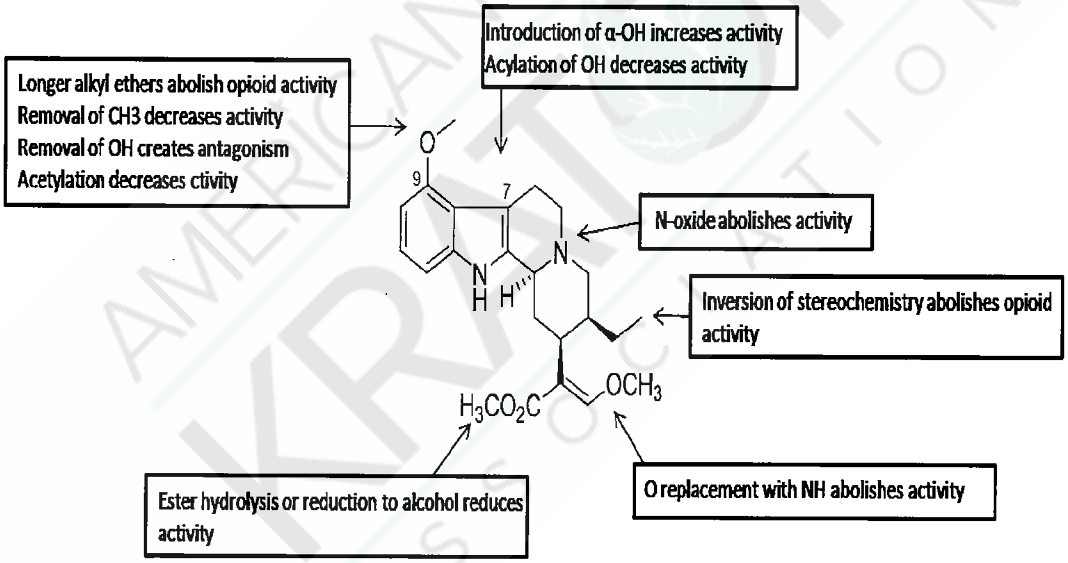
(57) **ABSTRACT**

Kratom (*Mitragynia speciosa* korth) is recognized increasingly as a remedy for opioid withdrawal by individuals who self-treat chronic pain and/or generalized substance abuse. For example, opioid withdrawal from an abrupt cessation of opiate abuse may be self-managed by using Kratom. Further, high-throughput molecular screening identified that a major component of Kratom (i.e., for example, mitragyinine) displayed high binding affinity at mu, delta and kappa opiate receptors. The present invention contemplates that Kratom extract may also be useful for the treatment of other addictive drugs besides opiate derivatives.


Longer alkyl ethers abolish opioid activity
Removal of CH3 decreases activity
Removal of OH creates antagonism
Acetylation decreases ctivity
Introduction of α-OH increases activity
Acylation of OH decreases activity
N-oxide abolishes activity
Inversion of stereochemistry abolishes opioid activity
O replacement with NH abolishes activity
Ester hydrolysis or reduction to alcohol reduces activity
9
7
N
N
H
H
H_3CO_2C
OCH_3



Panel A.


Introduction of α-OH increases activity
Acylation of OH decreases activity
Longer alkyl ethers abolish opioid activity
Removal of CH3 decreases activity
Removal of OH creates antagonism
Acetylation decreases ctivity
O
9
7
N
NH
H
N-oxide abolishes activity
Inversion of stereochemistry abolishes opioid activity
H_3CO_2C
OCH_3
Ester hydrolysis or reduction to alcohol reduces activity
O replacement with NH abolishes activity

Panel B.

FIGURE 1

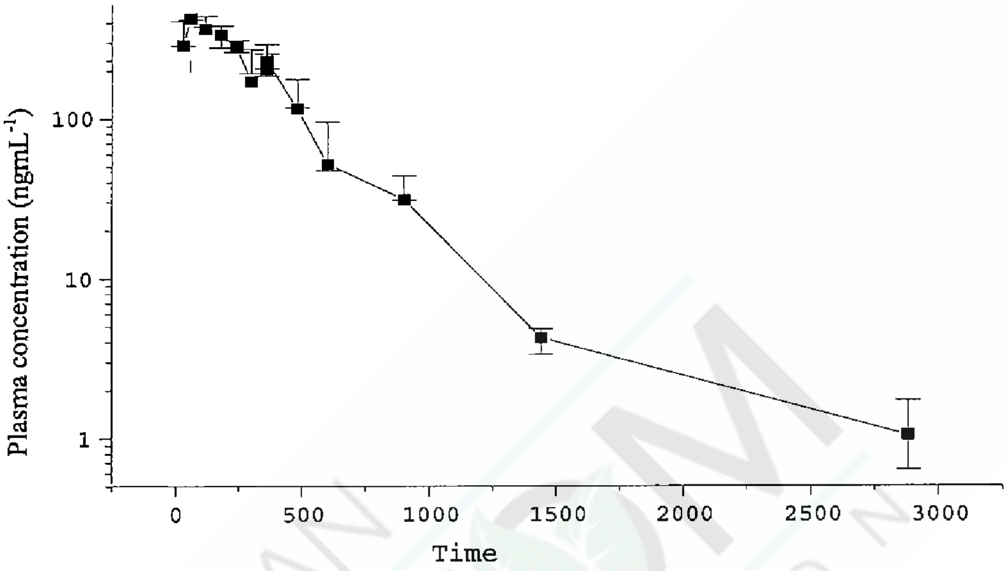

Plasma concentration (ngmL^{-1})
100
10
1
0
500
1000
1500
2000
2500
3000
Time

FIGURE 2

Parameter	Units	Mean ± S.D.	S.E.
C_{max}	(ng/mL)	423.68 ±174.80	61.79
t_{max}	(min)	75.58 ±34.36	12.11
$t_{1/2\ a}$	(min)	16.97 ± 16.13	5.70
K_a	(1/min)	0.041 ± 0.028	0.009
$t_{1/2}$	(min)	231.24 ± 85.70	30.30
K_{el}	(1/min)	0.0030 ± 0.0009	0.0003
$AUC^{0-?}$	(μg.min/mL)	188.98 ± 54.87	19.40
V_d/f	(L/kg)	37.90 ± 15.32	5.41
Cl/f	(L/h.kg)	105.84 ± 20.46	7.23

FIGURE 3

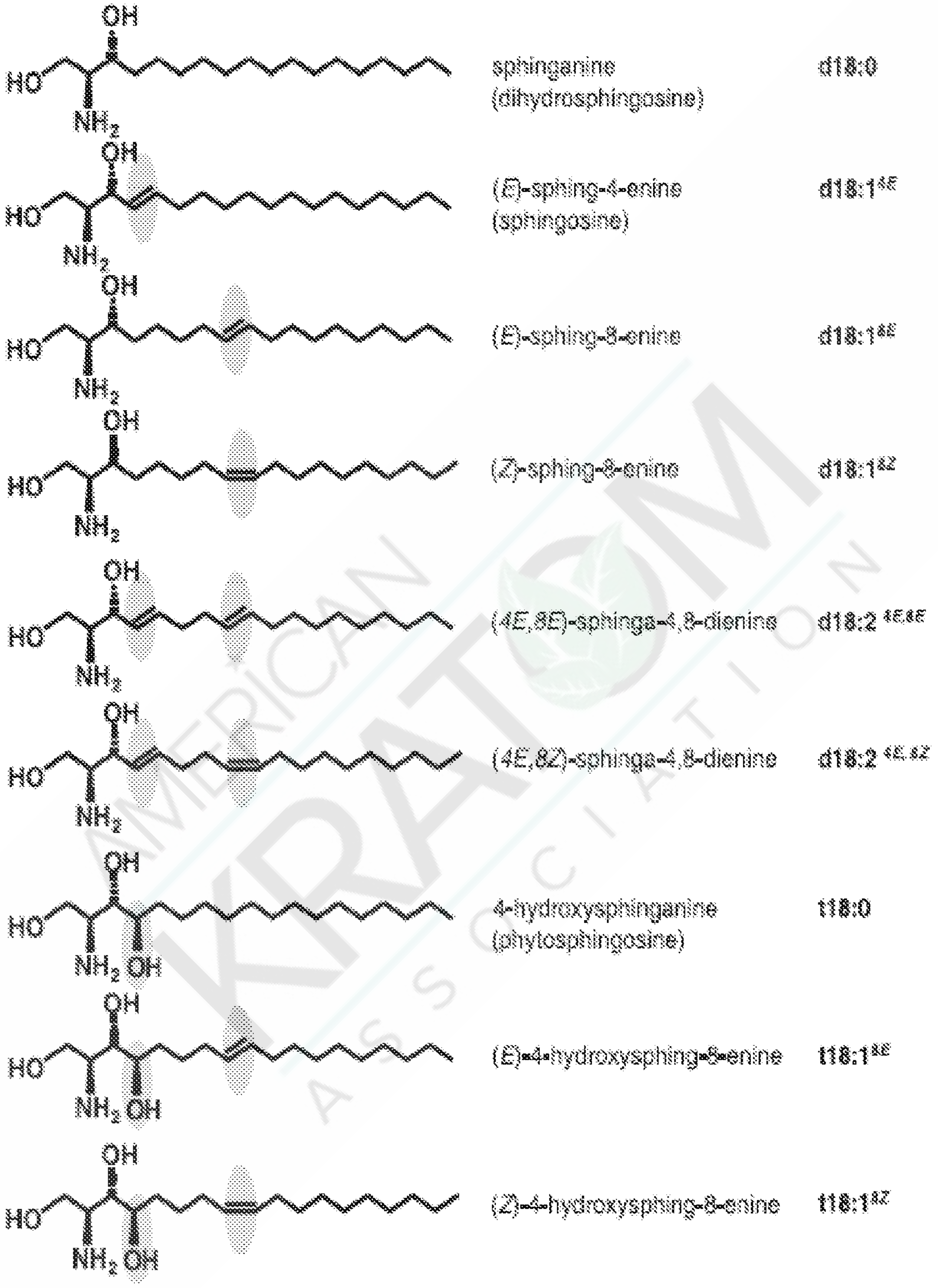
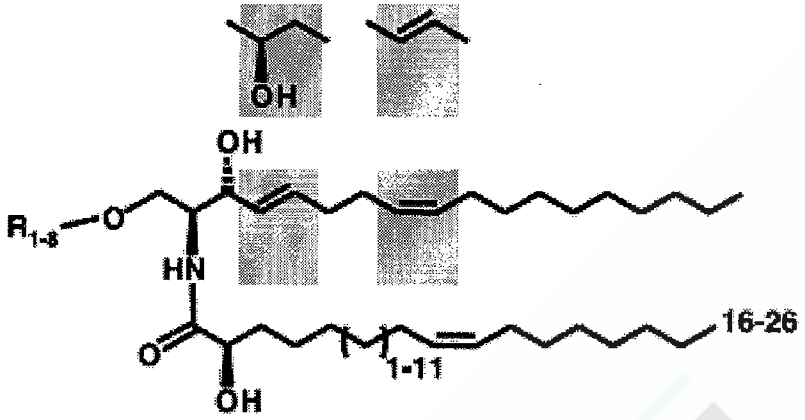

OH
HO
NH_2
sphinganine
(dihydrosphingosine)
d18:0
(*E*)-sphing-4-enine
(sphingosine)
$d18:1^{4E}$
(*E*)-sphing-8-enine
$d18:1^{8E}$
(*Z*)-sphing-8-enine
$d18:1^{8Z}$
(*4E*,*8E*)-sphinga-4,8-dienine
$d18:2^{4E,8E}$
(*4E*,*8Z*)-sphinga-4,8-dienine
$d18:2^{4E,8Z}$
4-hydroxysphinganine
(phytosphingosine)
t18:0
(*E*)-4-hydroxysphing-8-enine
$t18:1^{8E}$
(*Z*)-4-hydroxysphing-8-enine
$t18:1^{8Z}$

FIGURE 4



Ceramides
R_1 = H-

Cerebrosides
R_2 = β-D-Man-
R_3 = β-D-Glu-
R_4 = [β-D-Man(1,4)]$_{1-3}$-β-D-Glu-
R_5 = β-D-Glu(1,4)-[β-D-Man(1,4)]$_{1-2}$-β-D-Glu-

GIPC (phytoglycolipids)
R_6 = α-D-GluN(1,4)-α-D-GluA(1,2)-*m*-Ino(1-P)-
R_7 = β-D-Gal(1,4)-α-D-GluNac(1,4)-α-D-GluA(1,2)-*m*-Ino(1-P)-
R_8 = [α-D-Man(1,2)]-α-D-GluN(1,4)-α-D-GluA(1,6)-*m*-Ino(1-P)-

FIGURE 5

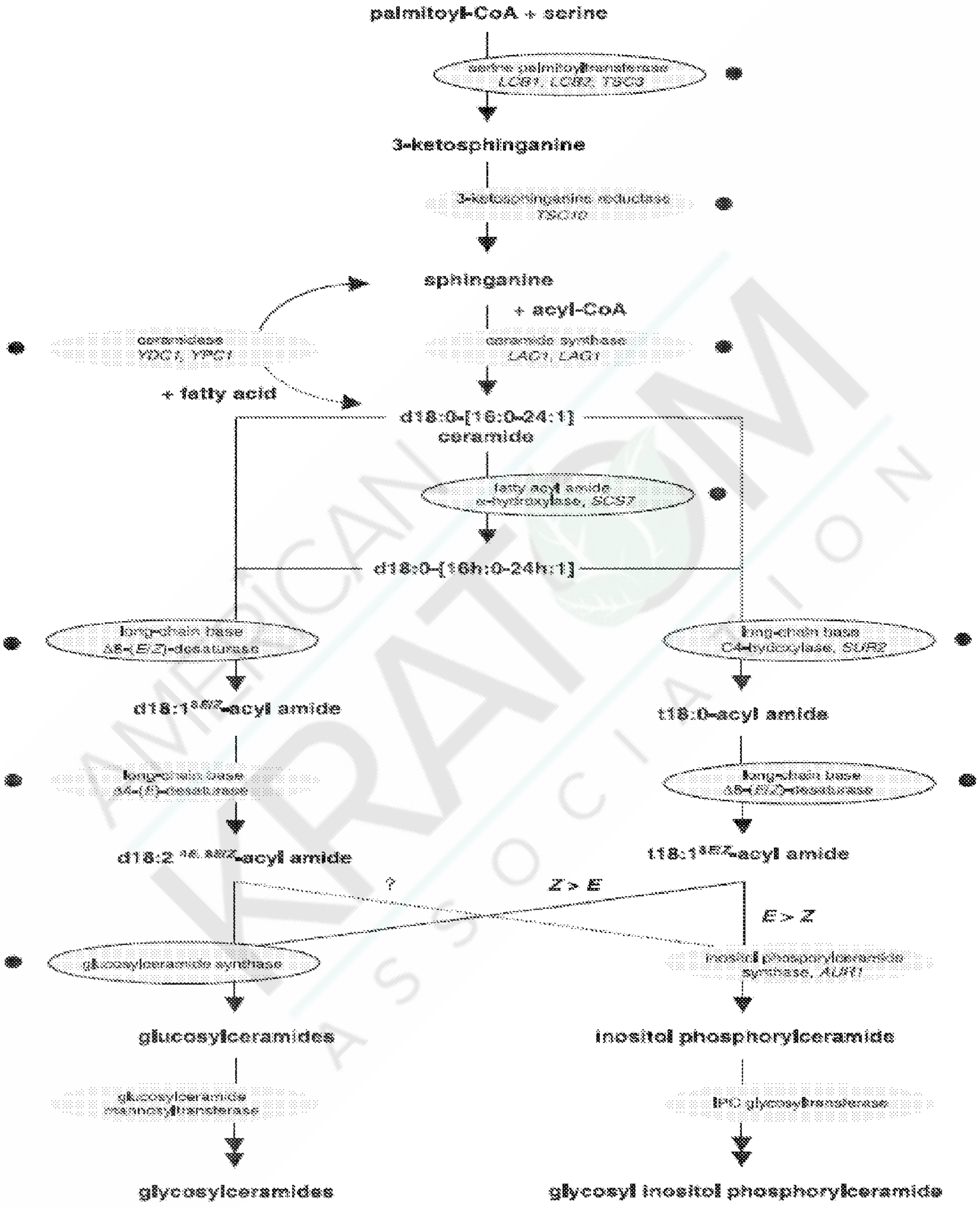

palmitoyl-CoA + serine
serine palmitoyltransferase
LCB1, LCB2, TSC3
3-ketosphinganine
3-ketosphinganine reductase
TSC10
sphinganine
+ acyl-CoA
ceramidase
YDC1, YPC1
ceramide synthase
LAC1, LAG1
+ fatty acid
d18:0-[16:0-24:1]
ceramide
fatty acyl amide
α-hydroxylase, SCS7
d18:0-[16h:0-24h:1]
long-chain base
Δ8-(E/Z)-desaturase
long-chain base
C4-hydroxylase, SUR2
d18:1 8E/Z-acyl amide
t18:0-acyl amide
long-chain base
Δ4-(E)-desaturase
long-chain base
Δ8-(E/Z)-desaturase
d18:2 Δ4, 8E/Z-acyl amide
t18:1 8E/Z-acyl amide
?
Z > E
E > Z
glucosylceramide synthase
inositol phosphorylceramide
synthase, AUR1
glucosylceramides
inositol phosphorylceramide
glucosylceramide
mannosyltransferase
IPC glycosyltransferase
glycosylceramides
glycosyl inositol phosphorylceramide

FIGURE 6

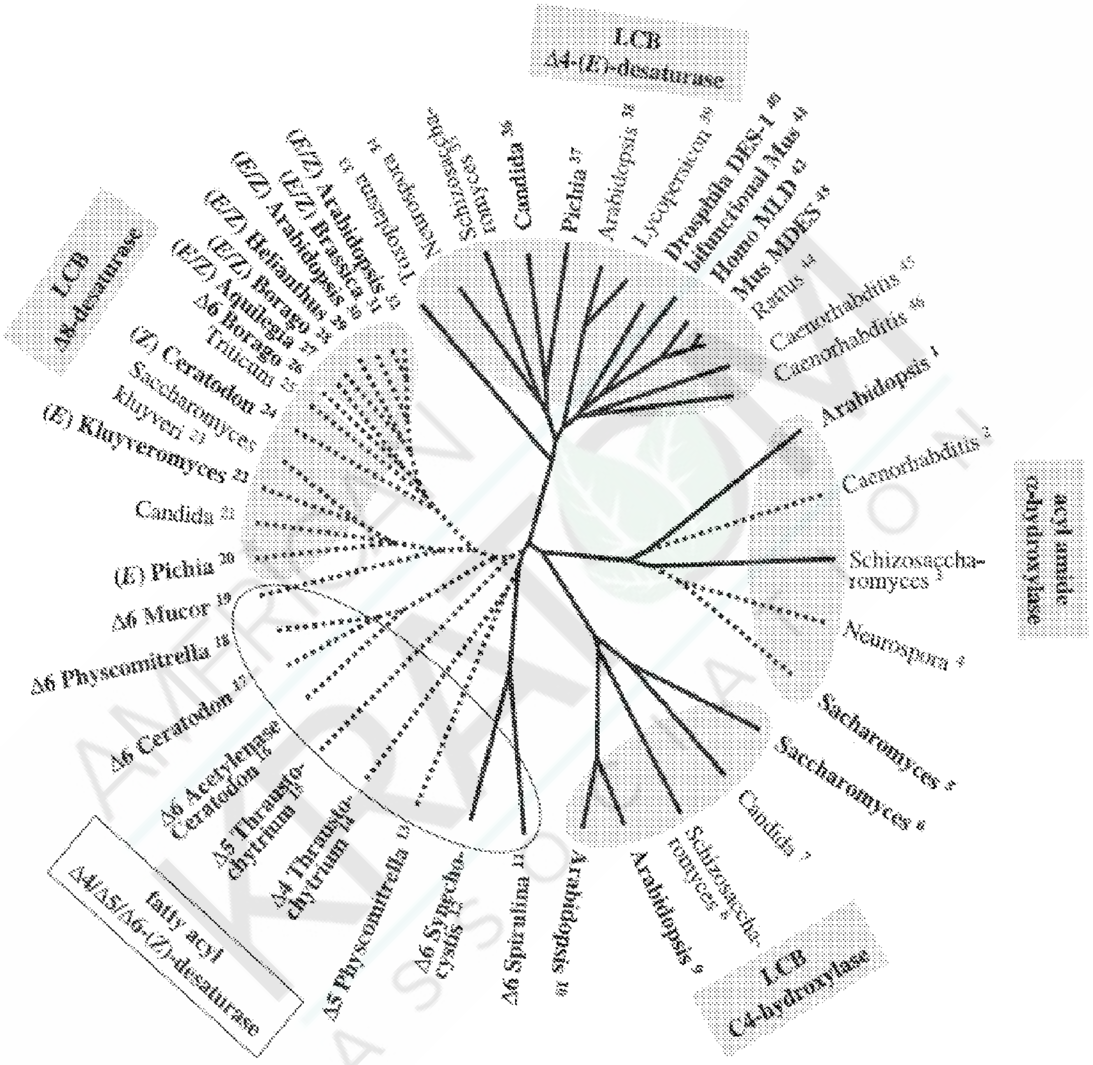

LCB
Δ4-(E)-desaturase
Arabidopsis 38
Lycopersicon 39
Drosophila DES-1 40
bifunctional Mus 41
Homo MLD 42
Mus MDES 43
Rattus 44
Caenorhabditis 45
Caenorhabditis 46
Arabidopsis 1
Caenorhabditis 2
acyl amide
α-hydroxylase
Schizosaccharomyces 3
Neurospora 4
Sacharomyces 5
Saccharomyces 6
Candida 7
Schizosaccharomyces 8
Arabidopsis 9
LCB
C4-hydroxylase
Arabidopsis 10
Δ6 Spirulina 11
Δ6 Synechocystis 12
Δ5 Physcomitrella 13
Δ4 Thraustochytrium 14
Δ5 Thraustochytrium 15
Δ6 Acetylenase Ceratodon 16
fatty acyl
Δ4/Δ5/Δ6-(Z)-desaturase
Δ6 Ceratodon 17
Δ6 Physcomitrella 18
Δ6 Mucor 19
(E) Pichia 20
Candida 21
(E) Kluyveromyces 22
Saccharomyces kluyveri 23
(Z) Ceratodon 24
Triticum 25
Δ6 Borago 26
(E/Z) Aquilegia 27
(E/Z) Borago 28
(E/Z) Helianthus 29
(E/Z) Arabidopsis 30
(E/Z) Brassica 31
(E/Z) Arabidopsis 32
LCB
Δ8-desaturase
Tropaeolum 33
Neurospora 34
Schizosaccharomyces 35
Candida 36
Pichia 37

FIGURE 7

METHODS FOR TREATING WITHDRAWAL FROM ADDICTIVE COMPOUNDS

STATEMENT OF GOVERNMENTAL SUPPORT

[0001] This invention was made with government support awarded by: i) the National Institutes of Health (grant number NIH 022677); ii) the National Institute For Drug Abuse (grant numbers DA022677 and DA014929); and iii) the National Center for Research Resources (grant number P20RR021929). The government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] This invention is related to the field of drug addiction and substance abuse. In particular, the invention utilizes compounds that facilitate reversal of drug addiction by avoiding the expression of a withdrawal syndrome. For example, natural compounds may be produced from the Kratom (*Mitragyna speciosa* Korth) leaf. Compounds isolated from Kratom leaf extracts may be capable of allowing a patient to cease the administration of addictive compounds without experiencing physically debilitating withdrawal symptoms.

BACKGROUND

[0003] Drug addiction (i.e., for example, substance dependence) is usually exemplified by compulsively using a substance, despite its negative and sometimes dangerous effects. Drug abuse is commonly defined as using a drug excessively, or for purposes for which it was not medically intended. Behavioral patterns of addiction include compulsive drug-seeking, persistent abuse of substances despite the often dire consequences on social functioning and physical health, and the high probability of relapse even after prolonged drug-free periods.

[0004] The recent focus on the biological basis of drug addiction has provided evidence to support the hypothesis that behavioral manifestations for addiction are influenced by biological factors, and biological factors often produce behavioral changes that can further increase risk. The current understanding of the role of the dopaminergic, glutamatergic, epsilon-aminobutyric acidergic, and opioid receptor systems in the pathophysiology of addiction as well as the clinical implications of these systems for new and emerging treatments is improving. A variety of pharmacologic agents have been used in the treatment of substance abuse disorders and evaluated for safety, efficacy, and feasibility of use in different patient populations. Ivanov et al., "Neurorobiology and evidence-based biological treatments for substance abuse disorders" *CNS Spectr.* 11:864-877 (2006).

[0005] Nonetheless, clinical practice has not adequately dealt with the growing problem of treating subjects that have become addicted to compounds resulting from using either illicit drugs or legally prescribed pharmaceuticals. What is needed is a single agent capable of mitigating or otherwise treating addiction withdrawal where multiple agents with different CNS receptor binding affinities are presently required.

SUMMARY

[0006] This invention is related to the field of drug addiction and substance abuse. In particular, the invention utilizes compounds that facilitate reversal of drug addiction by avoiding the expression of a withdrawal syndrome. For example, natural compounds may be produced from the Kratom leaf. Compounds isolated from Kratom leaf extracts may be capable of allowing a patient to cease the administration of addictive compounds without experiencing physically debilitating withdrawal symptoms.

[0007] In one embodiment, the present invention contemplates a method, a) providing, i) a subject experiencing at least one withdrawal symptom induced by at least one addictive compound; ii) a Kratom extract capable of reducing or preventing the at least one withdrawal symptom; and b) administering the Kratom extract to the subject under conditions such that the at least one withdrawal symptom is prevented and/or reduced. In one embodiment, the addictive compound comprises an opiate compound. In one embodiment, the addictive compound comprises an ethanol compound. In one embodiment, the addictive compound comprises a cocaine compound. In one embodiment, the addictive compound comprises a cannabinoid compound. In one embodiment, the opiate compound comprises a prescribed opiate compound. In one embodiment, the Kratom extract comprises mitragynine. In one embodiment, the Kratom extract comprises a mitragynine derivative. In one embodiment, the mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine. In one embodiment, the withdrawal symptom comprises a craving induced by the addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

[0008] In one embodiment, the present invention contemplates a method, a) providing, i) a subject repeatedly exposed to at least one compound, wherein the subject is at risk of experiencing at least one withdrawal symptom; ii) a Kratom extract capable of reducing or preventing the at least one withdrawal symptom; b) administering the Kratom extract as a substitute for the at least one compound under conditions such that the at least one withdrawal symptom is prevented or reduced. In one embodiment, the administering further comprises a regimen of decreasing said Kratom extract over a predetermined length of time. In one embodiment, the addictive compound comprises an opiate compound. In one embodiment, the addictive compound comprises an ethanol compound. In one embodiment, the addictive compound comprises a cocaine compound. In one embodiment, the addictive compound comprises a cannabinoid compound. In one embodiment, the opiate compound comprises a prescribed opiate compound. In one embodiment, the Kratom extract comprises mitragynine. In one embodiment, the Kratom extract comprises a mitragynine derivative. In one embodiment, the mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine. In one embodiment, the withdrawal symptom comprises a craving induced by the addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

[0009] In one embodiment, the present invention contemplates a method, a) providing, i) a subject experiencing at least one withdrawal symptom induced by at least one addictive compound; ii) a composition comprising mitragynine, wherein the composition is capable of reducing or preventing the at least one withdrawal symptom; and b) administering the composition to the subject under conditions such that the at least one withdrawal symptom is prevented and/or reduced. In one embodiment, the addictive compound comprises an opiate compound. In one embodiment, the addictive compound comprises an ethanol compound. In one embodiment, the addictive compound comprises a cocaine compound. In one embodiment, the addictive compound comprises a cannabinoid compound. In one embodiment, the opiate compound comprises a prescribed opiate compound. In one embodiment, the composition comprises a mitragynine derivative. In one embodiment, the mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine. In one embodiment, the withdrawal symptom comprises a craving induced by the addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

[0010] In one embodiment, the present invention contemplates a method, a) providing, i) a subject repeatedly exposed to at least one addictive compound, wherein the subject is at risk of experiencing at least one withdrawal symptom; ii) a composition comprising mitragynine, wherein the composition is capable of reducing or preventing the at least one withdrawal symptom; and b) administering the composition to the subject under conditions such that the at least one withdrawal symptom is prevented and/or reduced. In one embodiment, the administering further comprises a regimen of decreasing said composition comprising mitragynine over a predetermined length of time. In one embodiment, the addictive compound comprises an opiate compound. In one embodiment, the addictive compound comprises an ethanol compound. In one embodiment, the addictive compound comprises a cocaine compound. In one embodiment, the addictive compound comprises a cannabinoid compound. In one embodiment, the opiate compound comprises a prescribed opiate compound. In one embodiment, the composition comprises a mitragynine derivative. In one embodiment, the mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine. In one embodiment, the withdrawal symptom comprises a craving induced by the addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

[0011] In one embodiment, the present invention contemplates a method, a) providing, i) a subject experiencing at least one opioid withdrawal symptom induced by at least one addictive opioid compound; ii) a composition comprising mitragynine, wherein the composition is capable of reducing or preventing the at least one withdrawal symptom; and b) administering the composition to the subject under conditions such that the at least one withdrawal symptom is prevented and/or reduced. In one embodiment, the opiate compound comprises a prescribed opiate compound. In one embodiment, the composition comprises a mitragynine derivative. In one embodiment, the mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine. In one embodiment, the withdrawal symptom comprises a craving induced by the addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

[0012] In one embodiment, the present invention contemplates a method, a) providing, i) a subject repeatedly exposed to at least one addictive opioid compound, wherein the subject is at risk of experiencing at least one opioid withdrawal symptom; ii) a composition comprising mitragynine, wherein the composition is capable of reducing or preventing the at least one withdrawal symptom; and b) administering the composition to the subject under conditions such that the at least one withdrawal symptom is prevented and/or reduced. In one embodiment, the administering further comprises a regimen of decreasing said composition comprising mitragynine over a predetermined length of time. In one embodiment, the opiate compound comprises a prescribed opiate compound. In one embodiment, the composition comprises a mitragynine derivative. In one embodiment, the mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine. In one embodiment, the withdrawal symptom comprises a craving induced by the addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

DEFINITIONS

[0013] The term "abuse" as used herein, refers to any intentional use of opioids outside of a physician's prescription for a bona fide medical condition, excluding accidental misuse.

[0014] The term "addiction" as used herein, refers to any neurobehavioral syndrome characterized by compulsive use, impaired control, tolerance, withdrawal, and continued use despite physical and psychological problems caused or exacerbated by use.

[0015] The term "dependence" as used herein, refers to any physiological state of adaptation to opioid analgesics, the absence of which produces signs and symptoms of withdrawal.

[0016] The term "tolerance" as used herein, refers to the need to use more opioid than previously to achieve the same effect. For example, the tolerance may comprise "functional" tolerance where the target tissue becomes relatively resistant to the drug (i.e., for example, by drug receptor up-regulation and/or decrease in receptor drug affinity). Alternatively, the tolerance may comprise "metabolic" tolerance where the drug is simply degrated faster (i.e, for example, by an increase in degradative enzymes).

[0017] The term "withdrawal" as used herein, refers to any predictable constellation of signs and symptoms resulting from abrupt removal of, or a rapid decrease in the regular dosage of an opioid.

[0018] The term "chronic pain" as used herein, refers to any persistent pain of greater than six (6) months' duration.

[0019] The term "drug" or "compound" as used herein, refers to any pharmacologically active substance capable of being administered which achieves a desired effect. Drugs or compounds can be synthetic or naturally occurring, non-peptide, proteins or peptides, oligonucleotides or nucleotides, polysaccharides or sugars.

[0020] The term "administered" or "administering" a drug or compound, as used herein, refers to any method of providing a drug or compound to a patient such that the drug or compound has its intended effect on the patient. For example, one method of administering is by an indirect mechanism using a medical device such as, but not limited to a catheter, applicator gun, syringe etc. A second exemplary method of administering is by a direct mechanism such as, local tissue administration (i.e., for example, extravascular placement), oral ingestion, transdermal patch, topical, inhalation, suppository etc.

[0021] The term "substitute for" as used herein, refers to switching the administration of a first compound or drug to a subject for a second compound or drug to the subject. For example, a Kratom extract may be substituted for an addictive compound such that a subject will be administered the Kratom extract instead of the addictive compound.

[0022] The term "repeatedly exposed" as used herein, refers to the administration of an addictive drug or compound to a subject on a regular schedule for a prolonged period of time. Such a schedule may comprise administration of a dose ranging between approximately once-to-twelve times per day for a time period lasting at least two successive days and may range over weeks, months, years, and even decades.

[0023] The term "at risk for" as used herein, refers to a medical condition or set of medical conditions exhibited by a patient which may predispose the patient to a particular disease or affliction. For example, these conditions may result from influences that include, but are not limited to, behavioral, emotional, chemical, biochemical, or environmental influences.

[0024] The terms "reduce," "inhibit," "diminish," "suppress," "decrease," "prevent" and grammatical equivalents (including "lower," "smaller," etc.) when in reference to the expression of any symptom (e.g., a withdrawal symptom) in an untreated addicted subject relative to a treated addicted subject, mean that the quantity and/or magnitude of the symptoms in the treated addicted subject is lower than in the untreated addicted subject by any amount that is recognized as clinically relevant by any medically trained personnel. In one embodiment, the quantity and/or magnitude of the symptoms in the treated addicted subject is at least 10% lower than, at least 25% lower than, at least 50% lower than, at least 75% lower than, and/or at least 90% lower than the quantity and/or magnitude of the symptoms in the untreated addicted subject.

[0025] The term "patient" or "subject", as used herein, is a human or animal and need not be hospitalized. For example, out-patients, persons in nursing homes are "patients." A patient may comprise any age of a human or non-human animal and therefore includes both adult and juveniles (i.e., children). It is not intended that the term "patient" connote a need for medical treatment, therefore, a patient may voluntarily or involuntarily be part of experimentation whether clinical or in support of basic science studies.

[0026] The term "affinity" as used herein, refers to any attractive force between substances or particles that causes them to enter into and remain in chemical combination. For example, an inhibitor compound that has a high affinity for a receptor will provide greater efficacy in preventing the receptor from interacting with its natural ligands, than an inhibitor with a low affinity.

[0027] The term "effective amount" as used herein, refers to a particular amount of a pharmaceutical composition comprising a therapeutic agent (i.e., for example, an opiate receptor agonist or antagonist) that achieves a clinically beneficial result.

[0028] The term "derived from" as used herein, refers to the source of a compound or drug. In one respect, a compound or drug may be derived from an organism or particular species. In another respect, a compound or drug may be derived from a larger macromolecular complex.

[0029] The term "pharmaceutically" or "pharmacologically acceptable", as used herein, refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human.

[0030] The term, "purified" or "isolated", as used herein, may refer to a composition or compound (i.e., for example, a chemical compound) that has been subjected to treatment (i.e., for example, chromatography) to remove various other components, and which composition substantially retains its expressed biological activity. Where the term "substantially purified" is used, this designation will refer to a composition in which the compound forms the major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or more of the composition (i.e., for example, weight/weight and/or weight/volume). A purified composition is not intended to mean that some trace impurities may remain.

[0031] As used herein, the term "substantially purified" refers to molecules, either compounds or drugs, that are removed from their natural environment, isolated or separated, and are at least 60% free, preferably 75% free, and more preferably 90% free from other components with which they are naturally associated. An "isolated compound or drug" is therefore a substantially purified compound or drug.

[0032] The term "small organic molecule" as used herein, refers to any molecule of a size comparable to those organic molecules generally used in pharmaceuticals. The term excludes biological macromolecules (e.g., proteins, nucleic acids, etc.). Preferred small organic molecules range in size from approximately 10 Da up to about 5000 Da, more preferably up to 2000 Da, and most preferably up to about 1000 Da.

[0033] The term "derivative" as used herein, refers to any chemical modification of a compound or drug. Illustrative of such modifications would be replacement of hydrogen by an alkyl, acyl, or amino group. For example, an opiate derivative would result in a different compound which retains essential biological characteristics such as binding affinity to an opiate receptor.

[0034] The term "biologically active" refers to any molecule or compound having structural, regulatory or biochemical functions.

[0035] The term "binding" as used herein, refers to any interaction between at least two different compounds. Binding may be reversible or irreversible. Such binding may be, but is not limited to, non-covalent binding, covalent bonding, ionic bonding, Van de Waal forces or friction, and the like.

[0036] The term "opiate compound" as used herein, refers to any compound having a morphine-based ring structure such that the structure-activity relationships of the compound results in physiological binding affinity to an opiate receptor (i.e., for example, K_d=10^{-3} to 10^{-12} M.). Such opiate compound may include, but are not limited to, heroin, opium, codeine, meperidine (i.e., for example, Demerol®), hydromorphone (i.e., for example, Dilaudid®), oxycontin, hydrocodone, oxycodone, fentanyl, morphine, methadone, and tramadol.

[0037] The term "ethanol compound" as used herein, refers to any compound or composition comprising ethanol (i.e, for example, CH_3CH_2OH). Ethanol is usually found in commercially available beverages including, but not limited to, beer, wine, and distilled liquors. An ethanol compound may comprise a variable concentration of ethanol ranging between 3%-100%, preferably ranging between 6%-50%, but more preferable ranging between 12%-25%.

[0038] The term "cocaine compound" as used herein, refers to any compound or composition comprising cocaine a derivative thereof, or an extract of a coca leaf. For example, cocaine may be processed into various compositions that comprise an altered chemical structure and/or crystalline structure. Such alterations may change pharmacokinetic parameters and/or usable routes of administration that may facilitate the development of cocaine addiction.

[0039] The term "nociceptive neurons" or "nociceptors" as used herein, refers to any neurons which respond to stimuli that are damaging or potentially damaging to the skin (e.g., intense pressure, high heat, and burning chemicals), and which thereby mediate pain.

[0040] The term "analgesia" or "relief from pain" as used herein, results from activation by opioid agonists of inhibitory opioid receptors on neurons in the nociceptive (pain) pathways of the peripheral and central nervous systems.

[0041] The term "psychological dependence" as used herein, refers to any psychological condition which manifests as an overpowering compulsion to continue taking an addictive drug (i.e., for example, an opioid).

[0042] The term "physical dependence" as used herein, refers to a state of physiologic adaptation to a drug, which may increase in intensity with increased dosage and duration of use of an addictive drug, and which may manifest in a withdrawal (abstinence) syndrome when the drug is discontinued or its effect is counteracted.

[0043] The term "tolerance" as used herein, refers to circumstances where the dosage of an addictive drug must be increased in order to obtain the initial effect.

BRIEF DESCRIPTION OF THE FIGURES

[0044] FIG. **1** presents Panel A showing the basic indole ring structure of components of an alkaloid Kratom extract and Panel B presenting the structure of mitragynine and identifies several structure-activity relationships.

[0045] FIG. **2** presents exemplary data showing plasma concentration-time curves for a single 20 mg/kg mitragyinine dose administered by oral gavage in Wistar rats.

[0046] FIG. **3** presents exemplary data demonstrating assay validation for the detection of mitragynine.

[0047] FIG. **4** presents exemplary structures of common long-chain bases from plants. All naturally occurring dihydroxy sphingoid bases have D-erythro and all trihydroxy sphingoid bases have D-ribo configuration. Additional double bonds and hydroxy groups characterizing the sphingoid bases derived from sphinganine are marked by grey background. While C_{18}-sphingoid bases are depicted, long-chain bases of different chain lengths occur in minor amounts. For example, in plant cerebrosides, the 8-(E)- and 8-(Z)-isomers of sphinga-4,8-dienine and 4-hydroxy-sphinga-8-enines are dominant, whereas sphingosine and 4-hydroxysphinganine, are predominant long-chain bases in animals and *S. cerevisiae.*

[0048] FIG. **5** presents exemplary structures of ceramide glycosides from plants. The ceramide backbones of plant sphingolipids show a large variability. These long-chain bases (LCBs) are presented in four embodiments (on grey background); i) hydroxylation; ii) (E)-desaturation at C-4, iii) (E)-desaturation at C-8; and iv) (Z)-desaturation at C-8. These LCB are linked to more than 10 different fatty acyl groups, which in turn vary in α-hydroxylation, chain length and Δ9-unsaturation. Cerebrosides are formed by glycosylation of the C1-hydroxy group of ceramide (R_1) yielding β-D-glucosyl and β-D-mannosyl ceramide (R_{2-3}). The glucosyl derivative may by elongated by sequential addition of up to three β-1,4-mannosyl residues resulting in oligosaccharides terminally capped by β-1,4-glucosyl residue (R_{4-5}). Glycosyl inositol phosphorylceramides (GIPC, phytoglycolipids) isolated from tobacco leaves (R_{6-7}) and corn kernels (R_8) carry a 1-phosphomyo-inositol residue linked via C2 and/or C6 to C1 of an a-glucuronosyl residue. Additional glycosyl derivatives with further galactosyl, mannosyl and fucosyl residues have been isolated from R_{7-8}.

[0049] FIG. **6** presents one embodiment of a pathway for sphingolipid biosynthesis in plants. Metabolites are shown in bold lettering, enzymes and their genes are included on grey background. Genes occurring in *S. cerevisiae* are given in the preferred designations listed in the *Saccharomyces* Genome Database. Functionally identified plant genes are marked by black framing of the enzymes. The presence of putative *A. thaliana* genes identified by comparison of their deduced amino acid sequences is indicated by a black dot next to the enzyme. The placement of some steps of sphingolipid synthesis, in particular of Δ4- and Δ8-LCB desaturation, the substrate specificities of the involved enzymes (i.e. free ceramide, cerebroside and GIPC) and the channelling of molecular ceramide species into complex sphingolipids are hypothetical (infra).

[0050] FIG. **7** illustrates a possible phylogram showing similarities between sphingolipid desaturases/hydroxylases and selected Δ4/Δ5/Δ6-fatty acyl desaturases. The regio-selectivities of lipid desaturases are indicated by Δ-numbers, their stereoselectivity by (E), (Z) or (E/Z) and the presence of a N-terminal cytochrome b5 fusion domain by dotted lines. All sphingolipid modifying enzyme groups are marked by grey background. Note the close similarity of the Δ6-fatty acyl desaturases from *B. officinalis* and *Mucor rouxii* to the Δ8-LCB desaturases. Functionally identified enzymes are highlighted by bold lettering. Superscripts refer to the following Accession numbers: [1]AF02104, [2]Z81038, [3]Z97209, [4]CAD21081, [5]Z49260, [6]AAA16608, [7]*C. albicans* ORF 6.4041 on contig 6-2307, [8]CAA21900, [9]AC013289, [10]AC012188, [11]X87094, [12]L11421, [13]unpublished, [14]AF489589, [15]AF489588, [16]AJ250734, [17]AJ250735, [18]AJ222980, [19]AF296076, [20]unpublished, [21]*C. albicans* genomic sequence on contig 6-1607, bases 2181430, [22]BAB93118, [23]BAB93117, [24]unpublished, [25]AF031194, [26]U79010, [27]AF406816, [28]AF133728, [29]×87143, [30]AJ224161, [31]AJ224160, [32]AC005397, [33]BAB58879, [34]*Neurospora crassa* genomic sequence on contig 9a58, bases 17916-16535, [35]T40333, [36]*C. albicans* genomic sequence on contig 6-2340, bases 7499-8611, [37]unpublished, [38]AAD17340, [39]AF466378, [40]AF466379, [41]AF466377, [42]AF466375, [43]AF466376, [44]NP_445775, [45]NP_501256, [46]NP_493549.

DETAILED DESCRIPTION OF THE INVENTION

[0051] This invention is related to the field of addiction and substance abuse. In particular, the invention utilizes compounds that reverse addiction while avoiding the expression of a withdrawal syndrome. For example, such natural compounds may be produced in the Kratom leaf. Compounds isolated from Kratom leaf extracts may be capable of allowing a patient to cease the administration of addictive compounds without experiencing physically debilitating withdrawal symptoms.

[0052] Drugs of abuse have in common the fact that they serve as biological rewards. As a result, any abused drug may be capable of activating specific endogenous brain neuronal pathways. Identification of such common neuronal pathways may find a common basis for the abuse liability of seemingly different addictive drugs. For example, two classes of abused drugs, psychomotor stimulants and opiates, may share a single brain reward mechanism. Some have suggested this common pathway to comprise dopamine-containing cells of the ventral tegmental area and their fiber projections to the cells of the nucleus accumbens. Morphine activates these cells possibly mediated via receptors imbedded in dopaminergic cell body membranes, or it may act on afferent terminals that synapse on the dopaminergic cell bodies or dendrites. Stimulants (i.e, for example, cocaine or amphetamine) may act at the terminals of the dopaminergic fibers to nucleus accumbens and perhaps other structures. The shared activation of the dopaminergic input to nucleus accumbens accounts for the behaviorally activating and the rewarding effects of both stimulants and opiates (the opiate stimulant action is not widely known because it is usually masked by depressant actions of opiates in other, antagonistic, brain circuits). The activation of dopaminergic systems may also account for amphetamine euphoria, cocaine euphoria, and opiate euphoria. Wise et al., "Brain mechanisms of drug reward and euphoria" *Psychiatr Med* 3:445-460 (1985). Recent studies, however, have identified the possible involvement of the specific opioid receptors in cocaine addiction and alcoholism. Kreek, M. J., "Opioid receptors: some perspectives from early studies of their role in normal physiology, stress responsivity, and in specific addictive diseases" *Neurochem Res*. 21:1469-88 (1996); and Kreek, M. J., "Opiates, opioids and addiction" *Mol Psychiatry* 1:232-54 (1996).

[0053] Drug abuse can lead to drug dependence and/or addiction. People who use drugs for pain relief may become dependent, although this is rare in those who don't have a history of addiction. A physical dependence on a substance (i.e., needing the drug to function) is not always part of the definition of addiction. Some drugs (for example, some blood pressure medications) don't cause addiction but do cause physical dependence. Other drugs may cause addiction without physical dependence. For example, cocaine withdrawal may not express symptoms like vomiting and chills (i.e., for example, physical symptoms) but usually involves depression (i.e., for example, behavioral symptoms).

[0054] The exact cause of drug abuse and dependence is not known. However, a person's genes, the action of a drug, peer pressure, emotional distress, anxiety, depression, and environmental stress all can be factors. Peer pressure can lead to drug use or abuse, but at least half of those who become addicted have depression, attention deficit disorder, post-traumatic stress disorder, or another psychological problem.

[0055] Symptoms of drug abuse may include, but are not limited to, a unexplained change in friends, withdrawn behavior, long unexplained periods away from home, lying, stealing, unusual interaction with legal authorities, compromised family relations, acting drunk or high (intoxicated), confusion, impossible to understand, unconsciousness, distinct changes in behavior and normal attitude.

[0056] Commonly abused substances include, but are not limited to, opiates and/or narcotics including, but not limited to, heroin, opium, codeine, meperidine (Demerol®), hydromorphone (Dilaudid®), and Oxycontin®; central nervous system (CNS) stimulants including, but not limited to, amphetamines, cocaine, dextroamphetamine, methamphetamine, methylphenidate (Ritalin®), caffeine or nicotine; CNS depressants including, but not limited to, barbiturates (i.e., for example, amobarbital, pentobarbital, or secobarbital), benzodiazepines (i.e., for example, Valium®, Ativan®, Xanax®), chloral hydrate, or paraldehyde; ethanol; hallucinogens including, but not limited to, lysergic acid diethylaminde (LSD), mescaline, psilocybin (i.e., for example, "magic" mushrooms), and phencyclidine (PCP or "Angel Dust"); or tetrahydrocannabinol (THC) as the active ingredient found in marijuana (*Cannabis sativa*) and hashish.

[0057] Drug withdrawal symptoms can occur when a person stops or reduces their use of a substance. Withdrawal symptoms vary, depending on the abused substance. When withdrawal symptoms begin depends on the length of time the drug normally stays within the body. Drug intoxication, overdose, and withdrawal can sometimes be life-threatening.

[0058] In one embodiment, the present invention contemplates a method for the treatment of withdrawal from an addictive drug. In one embodiment, the present invention contemplates a composition comprising a Kratom leaf extract. Although it is not necessary to understand the mechanism of an invention, it is believed that Kratom is a medicinal leaf harvested from *Mitragyna speciosa*, a tree native to Southeast Asia. In one embodiment, the Kratom leaf extract comprises mitragynine. See, FIG. **1**. Although it is not necessary to understand the mechanism of an invention, it is believed that mitragynine might be the most abundant alkaloid in Kratom leaves. The compound is believed to bind to, inter alia, μ- and κ-opiate receptors. Although it is not necessary to understand the mechanism of an invention, it is believed that a mitragynine-receptor interaction is presumably responsible for the treatment of addictive drug withdrawal.

I. Opioid Addiction and Withdrawal

[0059] In one embodiment, the present invention contemplates a method of treating opioid withdrawal syndrome using a Kratom extract or compounds derived from a Kratom extract. Opioid addiction can result from either illicit recreational use (where the subject obtains the drug "on the street") or from a legal drug prescription received from a medical doctor. Such legal prescriptions are routinely provided for conditions including, but not limited to, chronic pain. Pain therapy routinely involves the prescription of opioid compounds, wherein natural compounds may provide a reversal of the addiction phenomenon while sparing the patient the clinical manifestations of a classical withdrawal syndrome.

[0060] Symptoms of opiate and/or narcotic use include, but are not limited to, needle marks on the skin in some cases (called "tracks"), scars from skin abscesses, rapid heart rate, small pupils (pinpoint), relaxed and/or euphoric state ("nodding"), coma, respiratory depression leading to coma, and death in high doses.

[0061] Symptoms of opiate and/or narcotic withdrawal include, but are not limited to, anxiety and difficulty sleeping, sweating, goose bumps (piloerection), runny nose (rhinorrhea), stomach cramps and/or diarrhea, enlarged (dilated) pupils, nausea and/or vomiting, excessive sweating, increase in blood pressure, pulse, and/or temperature.

[0062] The World Health Organization (WHO) analgesic ladder principle continues to serve as an educational tool in the efforts by WHO in collaboration with the World Federation of Societies of Anaesthesiologists (WFSA) and The International Association for the Study of Pain (IASP) to increase knowledge of pharmacological pain therapy and increase availability of essential opioid analgesics worldwide. Opioids differ in pharmacodynamics and pharmacokinetics, and patients have different pharmacogenetics and pain mechanisms. Sequential trials of the increasing numbers of available opioid drugs are therefore appropriate when oral morphine fails.

[0063] Controversies continue concerning diagnosis and handling of: i) opioid-insensitive pain in both chronic cancer and chronic non-cancer pain; ii) opioid-induced neurotoxicities; iii) risks of tolerance, addiction, pseudo-addiction; iv) methods for improving effectiveness and decreasing adverse effects of long-term opioid therapy; and v) treating breakthrough pain with immediate release oral and transmucosal opioids. Consensus guidelines have recently been developed in the Nordic countries concerning the ethical practice of palliative sedation when opioids and other pain-relieving therapies fail in patients soon to die. Guidelines for long-term treatment with strong opioids of chronic non-cancer-related pain are also being developed in the Nordic countries, where very diverging traditions for the usage of such therapy still exist.

[0064] Opioid analgesics remain highly effective modalities for the treatment of chronic pain, but their long-term administration is associated with the development of opioid misuse, abuse, dependence and addiction, the incidence of which is increasing. Fishbain et al., "Drug abuse, dependence, and addiction in chronic pain patients" *Clin J Pain* 8:77-85 (1992).

[0065] Developing pharmacological treatments for opioid dependence and withdrawal that possess potential added benefits over the existing interventions is of great importance. Opioid replacement therapies commonly involve methadone or Suboxone® (a buprenorphine/naloxone co-formulation). Both of these therapies suffer from significant limitations. Dramatic increases in accidental deaths from methadone correlate with increased rates of its prescription.[4]Suboxone®, a more recent therapeutic development, suffers from poor penetration into communities of opioid addicts because of severe regulatory restriction on the number of prescriptions that physicians may write. Furthermore, Suboxone® is contraindicated in individuals who abuse Oxycontin® or fentanyl patches, two of the most commonly abused prescription opioid analgesic formulations. Lastly, Suboxone®, a treatment for addiction, has poor acceptance among individuals who self-treat chronic pain with opioid analgesics purchased from Internet pharmacies, a population who does not view themselves as addicts.[1] An urgent need therefore exists to develop effective and safe pharmacologic interventions for prescription opioid analgesic addiction.

[0066] Abuse of, and addiction to, opioid agents is not a new phenomenon.[10] What is unprecedented, however, is the scale, range and growth of the abuse of opioid analgesic agents. In addition, a marked increase in the therapeutic use of opioid medications has been observed in the United States along with an even greater increase in problems associated with these agents' use.[11] The surging use of opioids and associated problems is particularly concerning because it represents an expanded pathway to opioid addiction.[12, 13]

[0067] Between 1999 and 2002, the number of opioid analgesic poisonings on death certificates increased 91.2%, while heroin and cocaine poisonings increased 12.4% and 22.8%, respectively. The increase in deaths generally matched the increase in sales for each type of opioid.[4] In 2002 ~4.7% of American household residents over age 12 had abused an opioid medication; 13.7% of these individuals met DSM-IV criterion for a diagnosis of opioid abuse disorder.[14, 15] Hydrocodone has been reported to rank as the second-most abused substance among college students, a population noted for exploratory substance use. Risk factors associated with tolerance, dependence, and abuse of opioid analgesics are poorly understood.[13, 16-18] Prescription opioid analgesics that are commonly abused in the United States include, but are not limited to, hydrocodone, oxycodone, hydromorphone, codeine, fentanyl, morphine, methadone, and tramadol.

[0068] Further, methadone deaths increased nearly 500% between 1999 and 2005.[19] Dramatic increases in deaths from methadone correlate with increased rates of prescription.[4] Most deaths occur soon after initiation of methadone treatment in chronic pain patients, and not from methadone-based treatment of heroin addiction.[4] Clusters of methadone deaths in North Carolina and New Mexico overlay an increasing baseline of methadone deaths nationally.[20, 21] Suboxone® produces life-threatening toxicity as well. Ingestion of Suboxone® as a result of normal childhood exploratory behavior has led to coma, apnea, and severe adverse effects including cortical blindness. Importantly, children need not ingest a Suboxone® tablet; merely putting a tablet in the mouth is sufficient to produce life-threatening toxicity.[22]

[0069] One reason for the higher death rate among opioid dependent individuals with chronic pain is because they do not view themselves as addicts. In their mind, addicts cannot function because they use drugs. The opposite, however, is true. An addict must use the drug in order to function (i.e., feel normal). It is in the absence of drug use where an addict begins to have trouble functioning and ultimately encounters symptoms of a withdrawal syndrome.

[0070] Opioid-dependent chronic pain suffers, particularly those who self-prescribe hydrocodone and/or oxycodone, also believe that they function because they use drugs. To the extent this is true, methadone is a highly unacceptable medication because of its association with heroin addict and treatment. Suboxone® has met with greater acceptance by this population, but the limitation on the number of prescriptions that a clinician may write has dampened the enthusiasm of prescription opioid abusers for this therapy.

II. Cocaine Addiction and Withdrawal

[0071] In one embodiment, the present invention contemplates a method of treating cocaine withdrawal syndrome using a Kratom extract or compounds derived from a Kratom extract. Cocaine addiction results primarily from illicit recreational use where the subject obtains the drug "on the street", wherein natural compounds may provide a reversal of the addiction phenomenon while sparing the patient the clinical manifestations of a classical withdrawal syndrome.

[0072] Symptoms of cocaine use includes, but are not limited to, exaggerated feeling of well-being (euphoria), dilated pupils, fast heart rate, or restlessness and/or hyperactivity.

[0073] Symptoms of cocaine withdrawal includes, but are not limited to, fatigue and/or malaise, depression, and very clear and/or unpleasant dreams.

[0074] Many studies have shown interactions between mu-opiates and the mesolimbic dopamine (DA) system. For example, mu-opiate receptor antagonists have been reported to modulate the rate of cocaine self-administration. Characterization and localization the effect of opiate receptor blockade on the reinforcing effects of cocaine was studied using the mu-opiate irreversible antagonist beta-funaltrexamine (betaFNA). Microinjection of betaFNA into the ventral tegmental area (VTA) or the nucleus accumbens (NAcc) had no effect on cocaine self-administration under a fixed ratio (FR) schedule of reinforcement. However, blockade of opiate receptors in both brain regions did attenuate responding for cocaine maintained by a progressive ratio (PR) schedule. Administration of betaFNA in the dorsal striatum had no effect under either schedule condition. These data suggest that endogenous opiate systems within the mesolimbic DA system modulate the reinforcing effects of cocaine; however, this modulation seemed to be schedule dependent. Ward et al., “Beta-funaltrexamine affects cocaine self-administration in rats responding on a progressive ratio schedule of reinforcement” *Pharmacol Biochem Behav.* 75:301-307 (2003).

[0075] Numerous reports support evidence that dopaminergic mesolimbic pathways interact with opioid systems to influence the reinforcing properties of cocaine. For example, withdrawal from chronic administration of cocaine in rats causes an upregulation of mesocorticolimbic mu-opioid receptors during early stages. Prolonged cocaine abstinence was addressed by treating rats with cocaine or saline (control) intermittently (1 mg/kg, i.v., every 12 min for 2 h daily) for 10 days followed by a 10- or 20-day withdrawal period following which a quantitative in vitro autoradiographic analysis of 14 brain regions with (125)I-DAMGO was performed. A separate group of animals received two consecutive cycles of the 10-day cocaine/10-day withdrawal regimen. Only the group that participated in the two consecutive cycles showed a significant effect of cocaine treatment by a downregulation of mu-opiate receptors in; i) the limbic cortical layer 3 (17% lower than saline-treated controls, P=0.03); ii) the core of the nucleus accumbens (16% decrease, P=0.05); and iii) the nucleus of the diagonal band (18% decrease, P=0.05). Sharpe et al., “Autoradiographic evidence that prolonged withdrawal from intermittent cocaine reduces mu-opioid receptor expression in limbic regions of the rat brain” *Synapse* 37:292-297 (2000).

[0076] Opiate-related molecular changes were found in the neostriatum of human subjects who died with a history of cocaine abuse and had detectable cocaine and/or cocaine metabolites at the time of death. Marked reductions in the levels of enkephalin mRNA and mu opiate receptor binding were found in the caudate and putamen, concomitant with elevations in levels of dynorphin mRNA and kappa opiate receptor binding in the putamen and caudate, respectively. Additionally, an imbalance in the activity of the two major striatal output pathways in cocaine users is implicated because peptide mRNA levels were reduced in enkephalinergic striatopallidal neurons and increased in dynorphinergic striatonigral neurons. Another imbalance, that of reductions of transmitter mRNA and receptor expression associated with euphoria (enkephalin and mu opiate receptors), together with elevations in mRNAs of transmitter systems associated with dysphoria (dynorphin and kappa opiate receptors), suggests a model of dysphoria and craving in the human cocaine addict brain. Hurd et al., “Molecular alterations in the neostriatum of human cocaine addicts” *Synapse* 13:357-369 (1993).

[0077] In vitro receptor autoradiography was used to determine the effect of chronic, continuous cocaine exposure of 2 weeks duration on [^{3}H]naloxone binding in various regions of rat brain. Although cocaine action in the central nervous system is usually associated with altered dopamine function, opiate receptor density (measured via [^{3}H]naloxone) was altered by chronic cocaine exposure in critical brain reward regions, including the nucleus accumbens, ventral pallidum, and lateral hypothalamus. Endogenous opioid activity at opiate receptors in these critical regions may be associated with the reinforcement induced by both cocaine and opiates. Hammer R. P., “Cocaine alters opiate receptor binding in critical brain reward regions” *Synaps.* 3:55-60 (1989).

III. Ethanol Addiction and Withdrawal

[0078] In one embodiment, the present invention contemplates a method of treating ethanol withdrawal syndrome using a Kratom extract or compounds derived from a Kratom extract. Ethanol addiction results primarily from recreational use where the subject obtains the drug legally but is unable to control their consumption patterns. In one embodiment, the present invention contemplates natural compounds that may provide a reversal of the addiction phenomenon while sparing the patient the clinical manifestations of a classical withdrawal syndrome.

[0079] Symptoms of alcohol use include, but are not limited to, slurred speech, lack of coordination, decreased attention span, and/or impaired judgment.

[0080] Symptoms of alcohol withdrawal include, but are not limited to, anxiety, shaking (tremors), seizures, increased blood pressure, pulse, and/or temperature, and/or delirium.

[0081] Alcoholism (i.e., for example, the chronic, excessive consumption of ethanol) has been recognized as a metabolic disease exhibiting the clinical features of craving for alcohol, loss of control over drinking, tolerance and physical dependence on alcohol, while both epidemiological and experimental studies have demonstrated that genetic factors may be important in determining whether an individual has a high or low vulnerability to develop alcoholism. Evidence also indicates that alcoholism is not characterized by a single gene/single allele inheritance pattern. Instead, multiple genes and environmental factors may interact to increase or decrease an individual’s vulnerability to become an alcoholic.

[0082] Current research is aimed at investigating whether certain behavioral, physiological and biochemical markers are highly associated with the incidence of alcoholism. One source of these potential biochemical markers include the endogenous opioid system, wherein the opiate system may mediate the reinforcing effects of ethanol. Current research is directed to: (a) the interactions of ethanol with the endogenous opioid system at the molecular level; (b) the existence of genetically determined differences in the response of the endogenous opioid system to ethanol between subjects at high and low risk for excessive ethanol consumption, as well as between lines of animals showing preference or aversion for ethanol solutions; (c) the decrease of alcohol consumption following pretreatment with opioid antagonists; and (d) the possible use of specific opioid receptor antagonists together with behavioral therapy to modify drinking behavior, to control craving and to prevent relapse. Gianoulakis et al., “Genetics of alcoholism: role of the endogenous opioid system” *Metab Brain Dis.* 9:105-131 (1994).

[0083] Some evidence indicates that the endogenous opioid system may play a role in maintaining alcohol drinking behavior. For example, the reinforcing properties of alcohol that lead to continued and repeated bouts of drinking may be due, in part, to alcohol-induced activation of the endogenous opioid system. Blocking the action of endogenous opioid peptides via administration of opioid antagonists significantly attenuates alcohol consumption in animals under a variety of experimental conditions. In clinical trials, opioid receptor antagonists decrease alcohol consumption, relapse rates, subjective high, and alcohol craving in outpatient alcoholics. Opioid receptor antagonists have been proposed to treat alcoholism and alcohol dependence. Froehlich et al., “Opioid involvement in alcohol drinking” *Ann NY Acad Sci.* 739:156-167 (1994); and Froehlich et al., “Recent developments in alcoholism:opioid peptides” *Recent Dev Alcohol.* 11:187-205 (1993).

[0084] The pleasant effects of alcohol intake may be partially mediated by mu-opiate receptors in the ventral striatum, a central area of the brain reward system. For example, blockade of mu-opiate receptors with naltrexone reduces the relapse risk among some but not all alcoholic individuals. Pronounced alcohol craving may occur among alcoholic individuals with a high availability of mu-opiate receptors in the brain reward system. In one study, the availability of central mu-opiate receptors was measured in vivo with positron emission tomography (PET) and the radioligand carbon 11-labeled carfentanil in the ventral striatum and compared with the severity of alcohol craving as assessed by the Obsessive Compulsive Drinking Scale (OCDS). After 1 to 3 weeks of abstinence, the availability of mu-opiate receptors in the ventral striatum, including the nucleus accumbens, was significantly elevated in alcoholic patients compared with healthy controls and remained elevated when 12 alcoholic patients had these levels measured 5 weeks later ($P<0.05$ corrected for multiple testing). Higher availability of mu-opiate receptors in this brain area correlated significantly with the intensity of alcohol craving as assessed by the OCDS. These data suggest that abstinent alcoholic patients displayed an increase in mu-opiate receptors in the ventral striatum, including the nucleus accumbens, which correlated with the severity of alcohol craving. Heinz et al., "Correlation of stable elevations in striatal mu-opioid receptor availability in detoxified alcoholic patients with alcohol craving: a positron emission tomography study using carbon 11-labeled carfentanil". *Arch Gen Psychiatry* 62:57-64 (2005).

IV. Cannabinoid Addiction and Withdrawal

[0085] In one embodiment, the present invention contemplates a method for treating tetrahydrocannabinol tolerance and/or dependence using a kratom extract. In one embodiment, the method comprises binding at least one component of the kratom extract to a cannabinoid receptor.

[0086] *Cannabis* is believed to be a widely used illicit drug in many western countries. Its psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), produces a variety of effects in animals and humans that are probably mediated by specific cannabinoid receptors in the brain and interactions with several neurotransmitter and neuromodulator systems. For instance, recent research has revealed an important mutual functional relationship between cannabinoids and endogenous opioid systems in mediating the pharmacological and behavioral actions produced by these agents including, but not limited to, drug reinforcement. Perinatal exposure to, and interactions between, cannabinoids and opioids might also have long-term behavioral consequences lasting into adulthood. Further, maternal exposure to THC may affect motivational properties of morphine in male and female adult rats, as measured by an intravenous opiate self-administration paradigm. Ambrosio et al., "The neurobiology of cannabinoid dependence: sex differences and potential interactions between cannabinoid and opioid systems" *Life Sci.* 65:687-694 (1999).

[0087] Advances in *cannabis* research have paralleled developments in opioid pharmacology whereby a psychoactive plant extract has elucidated novel endogenous signalling systems with therapeutic significance. Cannabinoids (CBs) are chemical compounds derived from *Cannabis*. The major psychotropic CB, delta-9-tetrahydrocannabinol (Delta(9)-THC), was isolated in 1964 and the first CB receptor (CB(1)R) was cloned in 1990. CB signalling occurs via G-protein-coupled receptors distributed throughout the body. Endocannabinoids are derivatives of arachidonic acid that function in diverse physiological systems. Neuronal CB(1)Rs modulate synaptic transmission and mediate psychoactivity Immune-cell CB(2) receptors (CB(2)R) may down-regulate neuroinflammation and influence cyclooxygenase-dependent pathways. Animal models demonstrate that CBRs play a fundamental role in peripheral, spinal, and supraspinal nociception and that CBs are effective analgesics. Clinical trials of CBs in multiple sclerosis have suggested a benefit in neuropathic pain. However, human studies of CB-mediated analgesia have been limited by study size, heterogeneous patient populations, and subjective outcome measures. Furthermore, CBs have variable pharmacokinetics and can manifest psychotropism. BCs are currently approved as antiemetics in chemotherapy and can be prescribed on a named-patient basis for neuropathic pain. Future selective peripheral CB(1)R and CB(2)R agonists will minimize central psychoactivity and may synergize opioid anti-nociception. Hosking et al., "Therapeutic potential of *cannabis* in pain medicine" *Br J Anaesth.* 101:59-68 (2008).

[0088] Interactions between opioid and cannabinoid receptors have been studied by epitope tagging mu, delta and kappa opioid receptors with *Renilla* luciferase and CB1 cannabinoid receptors with yellow fluorescent protein and examined for bioluminescence resonance energy transfer (BRET) signals. Coexpression and receptor-activated interaction of opioid receptors with cannabinoid receptors, was detected by an increase in BRET signal. Further, mu receptor-mediated signaling was attenuated by a CB1 receptor agonist; and this effect is reciprocal in that a CB1 mediated signal was attenuated by a mu receptor agonist. Rios et al., "mu opioid and CB1 cannabinoid receptor interactions: reciprocal inhibition of receptor signaling and neuritogenesis" *Br J Pharmacol.* 148: 385-386 (2006).

[0089] Interactions between opioid and cannabinoid systems have been proposed. For example, a modulatory interaction between opioid and cannabinoid systems may exist in the drug reinforcement. Jardinaud et al., "Tolerance to the reinforcing effects of morphine in delta 9-tetrahydrocannabinol treated mice" *Behav Brain Res.* 173:255-261 (2006). Functionality of the endogenous cannabinoid system undergoes relevant changes in reward-related brain areas in animal models of opiate addiction.

[0090] It has been suggested recently that the endocannabinoid system might be a component of the brain reward circuitry and thus play a role not only in cannabinoid tolerance, dependence, and withdrawal, but to other drugs of abuse as well. Changes in endocannabinoid ligands and their receptors have been observed in different brain regions (i.e., for example, those areas related to reinforcement processes) during morphine dependence. Rat brain contents of N-arachidonoylethanolamine (anandamide, AEA, an endocannabinoid) did not change in opiate-dependent animals, despite the presence of physical dependence. By contrast, a significant decrease in the specific binding for CB(1) receptors in the midbrain and the cerebral cortex of morphine-dependent rats was detected. These data suggest altered endocannabinoid transmission during morphine dependence in rats and may be useful in the treatment of morphine addiction. González et al., "Region-dependent changes in endocannabinoid transmission in the brain of morphine-dependent rats" *Addict Biol.* 8:159-166 (2003).

[0091] A relationship between the cannabinoid and opioid receptors in animal models of opioid-induced reinforcement has been reported. The acute administration of a selective central cannabinoid CB1 receptor antagonist (i.e., for example, SR141716A), blocked heroin self-administration in rats, as well as morphine-induced place preference and morphine self-administration in mice. Morphine-dependent animals injected with SR141716A exhibited a partial opiate-like withdrawal syndrome that had limited consequences on operant responses for food and induced place aversion. Additionally, the opioid antagonist naloxone precipitated a mild cannabinoid-like withdrawal syndrome in cannabinoid-dependent rats and blocked cannabinoid self-administration in mice. These results demonstrate a potential cross-interaction between opioid and cannabinoid systems in behavioral responses related to addiction and treatment of opiate dependence. Navarro et al., "Functional interaction between opioid and cannabinoid receptors in drug self-administration" *J Neurosci.* 21:5344-5350 (2001).

[0092] For example, the effects of SR141716A on the rewarding responses of morphine were evaluated in the place conditioning paradigm. SR141716A was able to antagonize the acquisition of morphine-induced conditioned place preference. SR141716A was co-administered with morphine for 5 days, and the withdrawal syndrome was precipitated by naloxone administration. A reduction in the incidence of two main signs of abstinence, wet dog shakes and jumping, was observed. In contrast, an acute injection of the CB(1) antagonist just before naloxone administration was unable to modify the incidence of the behavioural manifestations of the withdrawal, suggesting that only chronic blockade of CB(1) receptors is able to reduce morphine-induced physical dependence. Mas-Nieto et al., "Reduction of opioid dependence by the CB(1) antagonist SR141716A in mice: evaluation of the interest in pharmacotherapy of opioid addiction" *Br J Pharmacol.* 132:1809-1816 (2001).

[0093] By using a limited access heroin self-administration paradigm the cannabinoid CB(1) receptor antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride (SR141716A, 0.03-3.0 mg/kg) was shown to suppress heroin self-administration only in opiate-dependent rats but not in non-dependent animals. These results suggest that cannabinoid CB(1) receptor antagonists might be useful in the treatment of opiate addiction. Navarro et al., "Cannabinoid receptor antagonist reduces heroin self-administration only in dependent rats" *Eur J Pharmacol.* 501:235-237 (2004).

V. Kratom Opioid Derivatives

[0094] Kratom (*Mitragynia speciosa* korth) is a medicinal herb native to Southeast Asia (i.e, for example, Thailand) used traditionally by laborers to provide increased energy and to treat pain. It has more recently been used by recreational drug users for exploratory purposes. Kratom is legally an unscheduled drug and therefore is legal to own, possess, use, and sell. Recent studies have identified that a large population of individuals with chronic pain who are maintained on prescription opioid analgesics use Kratom as a natural opioid replacement therapy, and has been successfully used in place of methadone, buprenorphine, and other opioid-based treatment regimens. Furthermore, high throughput molecular screening for mitragynine, the predominant alkaloid in Kratom, has found that this molecule binds to central nervous system tissue mu (μ) and kappa (κ)-opiate receptors, α-2-adrenergic receptors, and 5-HT receptors. This data suggests that mitragyinine may have cumulative effects affecting many existing therapeutic approaches including, but not limited to; i) opioid replacement therapies (i.e, for example, methadoneibuprenorphine (at the μ and κ receptors); ii) clonidine therapies (at the α-2-adrenergic receptor); and iii) selective serotonin receptor inhibitor therapies (at 5-HT binding sites).

[0095] The concentration of mitragynine in Kratom tree leaves is highly variable and depends upon the phenotype of the tree as well as its location. Kratom was traditionally used as treatment for opium withdrawal, but reports of uncontrolled, compulsive use led to its criminalization in a number of countries, including Australia, Thailand, Malaysia, and Mynamar.[23, 24] Chronic use of Kratom has been associated with anorexia, weight loss, constipation and hyperpigmentation of the face.[25-27]

[0096] In one embodiment, the present invention contemplates a method for treating a subject exposed to opioid analgesic dependence, abuse and addiction. In one embodiment, the opioid dependence, abuse, and addiction is derived from clinical use of a prescription opioid compound. In one embodiment, the opioid dependence, abuse, and addiction is derived from recreational use of an illegal opioid compound. In one embodiment, the method comprises using Kratom (*Mitragyna speciosa* korth) derived extracts and/or compounds as an opioid replacement therapy to treat addiction to opioids including, but not limited to, oxycodone, fentanyl, hydrocodone, codeine, morphine, hydromorphone, or tramadol.

[0097] Much of the information related to Kratom pharmacological effects is derived from user interviews. The clinical effects of Kratom appear to be dose-dependent, where stimulant effects predominate at lower doses, while more traditional opioid sedative effects are more common at higher doses. Effects begin within 5-10 minutes of ingestion and persist for approximately 6 hours. Because it can be ingested in multiple forms (e.g., tea, capsule, or extract, among others), Kratom is a non-stigmatizing, yet an apparently effective, ersatz opioid replacement therapy that can bridge periods of analgesic abuse in highly opioid tolerant individuals.[28]

[0098] In addition to its pharmacologic profile, Kratom has several advantages which further enhance its utility over traditional treatment of opioid addiction, for example; i) Kratom use has never been associated with respiratory depression; ii) Kratom may obviate the morbidity and mortality associated with traditional opioid replacement therapy; iii) cessation from Kratom administration produces symptoms far less pronounced than those induced by cessation from other opioid replacement therapies; and iv) Kratom can be ingested in socially non-stigmatizing forms (i.e., for example, tea) that improve compliance during outpatient treatment of opioid addiction. Nonetheless, the tolerability and efficacy of Kratom in reducing opioid withdrawal in humans has not been clinically evaluated.

[0099] Kratom comprises at least twenty (20) indole alkaloids, two of which, mitragynine and 7-hydroxymitragynine, are structurally distinct from opiates.[2, 3, 35-38] Once isolated and purified, mitragynine binds CNS opioid receptors with high affinity. Using high throughput molecular screening of mitragynine, studies have demonstrated that mitragynine extensively inhibits radioligand binding at several relevant CNS receptor systems. Although mitragynine binds at several CNS receptors, only the dissociation constants for binding at opioid receptors have been determined. These pharmacologic effects appear to be responsible for the observed ability of Kratom to ameliorate and possibly extinguish opioid craving during abstinence.[28]

[0100] In one embodiment, the present invention contemplates a method comprising admninstering Kratom as replacement therapy for an addictive compound, and ceasing Kratom administration under conditions where withdrawal symptoms are reduced and/or prevented.

[0101] A. Kratom Extracts

[0102] Crystalline products were isolated from the leaves of *Mitragyna speciosa* that exhibits analgetic and antitussive properties. However, these products had failed to identify the Kratom extracts such as mitragynine for the treatment of opioid receptor based substance abuse. Beckett, "Speciofoline, An Alkaloid from *Mitragyna speciosa,"* U.S. Pat. No. 3,324,111; and Beckett et al., "Compositions Comprising An Alkaloid of *Mitragyna speciosa* and Methods of Using Same," U.S. Pat. No. 3,256,149 (both patents herein incorporated by reference).

[0103] Dosage-dependent effects of Kratom extract on animal physiology was recently reported. For example, high doses of Kratom extract decreased the increment of body weight similar to the effect of morphine. Chittrakarn et al., "Inhibitory Effects of Kratom Leaf Extact (*Mitragyna speciosa* Korth.) on the Rat Gastrointestinal Tract" *Journal of Ethnopharmacology* 116:173-178 (2007). Anecdotally, there have been suspicions that Kratom has traditionally been used as a substitute for opium when opium is unavailable, or by drug users who are trying to moderate their opium addiction (i.e., for example, self-medication). Opioid substance abuse during chronic alleviation of back pain has been treated using a Kratom derived extract. Boyer et al., Self-Treatment of Opioid Withdrawal Using Kratom, Addiction 103, 1048-1050 (2008).

[0104] Kratom components are believed to include, but are not limited to, mitragynine and 7-hydroxymitragynine, that have been reported to agonize the mu-opioid receptor with high affinity. Recent findings suggest that Kratom is purchased from internet sources by some of the 40 million Americans with chronic pain to self-manage opioid withdrawal. Boyer et al., "Self-treatment of opioid withdrawal with a dietary supplement Kratom" *Am J Addict* 16:352-356 (2007); Yamamoto et al., "Opioid receptor agonistic characteristics of mytragynine pseudoindoxyl in comparison with mitragyine derived from That medicine plant *Mytragyna speciosa" Gen Pharmacol* 33:73-81 (1999); Thongpradichote et al., "Identification of opioid receptor subtypes in antinociceptive actions of suprasinally administered Mitragynine in mice" *Life Sci* 62:1371-1378 (1998).

[0105] The data presented herein reports on a patient undergoing a protracted use of Kratom for chronic pain treatment and opioid replacement therapy. Boyer et al., "Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa* korth)" *Addiction* 103:1048-1050 (2008). It is currently believed that Kratom is gaining awareness as a 'natural' alternative to physician supervised opioid replacement therapy among individuals with chronic pain who are maintained on opioid analgesic agents. Boyer et al., "Self-treatment of opioid withdrawal with a dietary supplement, Kratom" *Am J Addict* 16:352-356 (2007). In one embodiment, the present invention contemplates a method wherein Kratom attenuates potentially severe opioid withdrawal, yet cessation of Kratom administration itself appears to be associated with modest abstinence symptoms. The pharmacological bases underlying this apparent paradox are uncertain. For example, mitragynine is theorized to stimulate contributions from adrenergic and serotonergic pathways that augment analgesia, but formal binding data have been obtained only for mu-, delta- and kappa opioid receptors. Takayama et al., "Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. *J Med Chem* 45:1949-1956 (2002); and Matsumoto et al., "Central antinoceptive effects of mitragynine in mice: contributions from noradrenergic and serotonergic systems" *Eur J Pharmacol* 317:75-81 (1996).

[0106] To delineate the in vitro pharmacology of Kratom more clearly, highthroughput molecular screening of mitragynine activity was conducted at central nervous system receptors (Novascreen Biosciences Corp., Hanover, Md., USA). These studies identified that mitragynine extensively inhibits radioligand binding at several central nervous system receptor systems (See, Table 1).

TABLE 1

Central nervous system receptor binding data for mitragynine.

Percentage inhibition of radioligand binding by mitragynine at selected receptor systems

Adenosine A2A: 65.66
Adrenergic (Alpha 2): 61.92
Dopamine D2: 54.22
Opioid, mu" 89.52
Opioid, kappa: 90.21
Opioid, delta: 7.00
Serotonin, 5HT2C: 58.77
Serotonin, 5HT7: 64.41

Dissociation constants for opioid receptor binding

Mu receptor: 204 ± 26 nM
Delta receptor: 2250 ± 120 nM
Kappa receptor: 455 ± 47 nM

[0107] The clinical implication of these results is that mu-opioid agonism may avert withdrawal symptoms, while kappa agonism attenuates reinforcement and produces aversion. Narita M. et al., "Regulations of opioid dependence by opioid receptor types" *Pharmacol Ther* 89:1-15 (2001). In addition, mitragynine, through its putative alpha-2 adrenergic agonist activity, may mimic adjunctive therapies for opioid withdrawal such as clonidine. Mitragynine, therefore, may exert several convergent pharmacological effects that could attenuate opioid withdrawal symptoms and blunt cravings.

[0108] Adverse effects induced by Kratom administration are poorly described. For example, respiratory depression, coma, pulmonary edema and death resulting from Kratom administration have not been reported despite an agonistic stimulation of mu-opioid receptors mediated by mitragynines. Furthermore, the protracted use of Kratom as a single therapy did not appear to produce any significant adverse effects in this patient; not until co-administration with modafinil was a potential adverse effect of Kratom identified. The exact mechanisms that contribute to seizure are undefined. The mitragynines, their metabolites or other components of Kratom could potentially exhibit proconvulsant properties similar to atypical opioids such as tramadol, the meperidine metabolite normeperidine and propoxyphene. Wills et al., "Drug- and toxin-associated seizures" *Med Clin North Am* 89: 1297-1321 (2005). Synergism between Kratom and modafinil might also produce seizure, but considering that modafinil is not likely to possess proconvulsant properties, this latter mechanism appears speculative. The relative risk/benefit ratio resulting from long-term Kratom administration is presently unknown.

[0109] Nonetheless, current trends of Kratom use may reflect an increasing public interest in obtaining alternative therapies for chronic medical problems. Wills et al., "Drug- and toxin-associated seizures" *Med Clin North Am* 89:1297-1321 (2005); Eisenberg et al., "Unconventional medicine in the United States. Prevalence, costs, and patterns of use" *N Engl J Med* 328:246-252 (1993). One reason for this increased interest is that some patients with chronic pain may misunderstand that formal drug treatment is reserved for users of illegal substances. Another reason is that many existing systems that treat chronic pain or problematic opioid use frequently under-prescribe analgesics, require treatment contracts, demand ongoing drug testing and/or otherwise stigmatize those who seek care. These disadvantages of current approaches to substance abuse treatment result in patient resistance to seek physician advice and treatment. Joranson et al., "Pain management, controlled substances, and state medical board policy: a decade of change" *J Pain Symptom Manag* 23:138-147 (2002).

[0110] Toxicity studies of lyophilized Kratom extraction into water have failed to produce respiratory depression.[34] Toxicity studies using mitragynine performed in the rat failed to identify respiratory depression, even at doses of 800 mg/kg administered via intraperitoneal dosing.[29]

[0111] Direct observation by addiction medicine experts of former injection drug abusers who abruptly ceased Kratom has revealed an abstinence syndrome with symptoms including, but not limited to, rhinorrhea, insomnia, lacrimation, lethargy, myalgias, or myoclonus.[27] Kratom withdrawal has not been associated with other common opiate withdrawal symptoms such as, gastrointestinal disturbances or severe malaise. In one embodiment, the present invention contemplates a method comprising administering Kratom to treat and/or prevent an opiate withdrawal syndrome following cessation of opiate use by a subject suffering from addiction and/or substance abuse.

[0112] In one embodiment, the present invention contemplates a method comprising self-treating a subject suffering from chronic pain with a Kratom extract. In one embodiment, the Kratom extract treatment does not develop tolerance in the subject. In one embodiment, the tolerance comprises functional tolerance. In one embodiment, the Kratom extract treatment does not develop a Kratom addiction in the subject.

[0113] B. Mitragynine

[0114] Mitragynine has been reported as a major alkaloidal component in *Mitragyna speciosa*. Other work has indicated that mitragynine exhibits analgesic activity mediated by opioid receptors. By utilizing this natural product as a lead compound, synthesis of some derivatives, evaluations of the structure-activity relationship, and surveys of the intrinsic activities and potencies on opioid receptors were performed with guinea pig ileum. For example, oxidative derivatives of mitragynine, (i.e., for example, mitragynine pseudoindoxyl and 7-hydroxymitragynine) were found to be opioid agonists with higher potency than morphine. Takayama et al., "Studies on the Synthesis and Opioid Agonistic Activities of Mitragynine-Related Indole Alkaloids: Discovery of Opioid Agonists Structurally Different from Other Opioid Ligands" *Journal of Medicinal Chemistry* 45:1949-1956 (2002). Further studies identified high affinity binding properties coupled with opioid antagonistic effects of mitragynine derivatives on individual opioid receptors, including, but not limited to, the μ-, δ- and κ-opiate receptors. Mitragynine and derivatives appear to bind to α_2-adrenergic as well as serotonergic receptors in the CNS. Kratom-derived compounds therefore integrate with the pharmacology of established treatments for opioid withdrawal such as methadone, buprenorphine, and clonidine. Importantly, the literature contains no reports of coma, respiratory depression or death from Kratom overdose.

[0115] It was reported that potent opioid agonistic activities of mitragynine and its analogues were found in in vitro and in vivo experiments during studies of mechanisms underlying the analgesic activity. Takayama, "Chemistry and Pharmacology of Analgesic Indole Alkaloids from the Rubiaceous Plant, *Mitragyna speciosa" Chemical and Pharmaceutical Bulletin* 52:916-928 (2004). Mitragynine structural features which differ from those of morphine were elucidated by pharmacological evaluation of the natural and synthetic derivatives. Among the mitragynine derivatives, 7-hydroxymitragynine, a minor constituent of *Mitragyna speciosa*, was found to exhibit potent antinociceptive activity in mice.

[0116] Mitragynine has also been reported as a partial opioid agonist producing similar effects to morphine. Alternatively, the mitragynine derivative, 7-hydroxymitragynine, has been reported to be more potent than morphine. Although it is not necessary to understand the mechanism of an invention, it is believed that mitragynine and 7-hydroxymitragyinie may activate supraspinal mu- and delta-opioid receptors, thereby explaining their use by chronic narcotics users to ameliorate opioid withdrawal symptoms". Babu et al., "Opioid Receptors and Legal Highs: Salvia divinorum and Kratom" *Clinical Toxicology* 46:146-152 (2008).

[0117] Pharmacological studies on mitragynine, the predominant alkaloid of Kratom, were first published in 1972.[29] Researchers who sought a novel analgesic with less abuse liability than the phenanthrene opioids conducted a battery of animal studies to investigate the analgesic potential and opioid actions of mitragynine. These studies demonstrated analgesic and antitussive properties comparable to codeine. Unlike codeine, mitragynine was not blocked by nalorphine and had much less respiratory depression. Further, mitragynine suppressed the opioid withdrawal syndrome. Moreover, mitragynine was active only via the oral and intraperitoneal routes of administration (in an equal ratio) but was inactive via the parenteral routes, a feature that diminished its abuse liability. The analgesic activity of mitragynine was again investigated in the tail-pinch and hot-plate tests resulting in antinociceptive activity that was completed abolished by naloxone, a pure opioid receptor antagonist. This indicated the involvement of supraspinal opioid receptors in the analgesic actions of mitragynine and a renewed interest in the pharmacology of this molecule.[30]

[0118] Mitragynine, in a manner similar to morphine, is believed to stimulate descending noradrenergic and serotonergic systems to produce analgesia.[30, 31] For example, the α_2-adrenoceptor antagonist, idazoxan, and the 5-HT receptor antagonist, cyproheptadine, antagonized the analgesic effects of mitragynine. This work indicated that mitragynine may stimulate the release of endogenous norepinephrine and serotonin, similar to the actions of other opioid ligands.[30, 31] In a companion study, the inhibition of electrically stimulated contraction in the guinea-pig ileum is reversed by naloxone, with the involvement of mu- and delta-opioid receptors identified through the use of subtype selective antagonists.[32]

[0119] The binding affinities for mitragynine at the three opioid receptors were determined using guinea pig brain membranes. This data indicated that mitragynine is a mu-opioid selective opioid ligand with a pKi value of 8.14±0.28 and a relative affinity of 88.7% for the mu- over the delta- and kappa-opioid receptors. The pKi values at the delta- and kappa-opioid receptor were 7.22±0.21 and 5.96±0.22, respectively. [33]

VI. Sphingolipids

[0120] In one embodiment, the present invention contemplates a composition comprising a kratom extract and a plurality of sphingolipids. In one embodiment, the sphingolipids comprise plant sphingolipids. In another embodiment, the present invention contemplates a method of reducing pain using a kratom extract comprising a plurality of sphingolipids, wherein the kratom sphingolipids increase the level of analgesia in comparison to a biomodal opioid agonist. In one embodiment, the sphingolipids comprise plant sphingolipids.

[0121] In one embodiment, the present invention contemplates a composition comprising mitragyinine and at least on sphingolipid. In one embodiment, the sphingolipid comprises a plant sphingolipid. In one embodiment, the present invention contemplates a method of reducing pain using mitragynine and at least one sphingolipid, wherein the sphingolipids increase the level of analgesia in comparison to mitragynine alone. In one embodiment, the sphingolipid comprises a plant sphingolipid.

[0122] A. Plant Sphingolipids

[0123] Plant sphingolipids comprise structural features differing from those found in animals and fungi. Sphingolipid modifications are found in plants and recent advances in the functional characterization of genes is gaining new insight into plant sphingolipid biosynthesis. Recent studies indicate that plant sphingolipids may be also involved in signal transduction, membrane stability, host-pathogen interactions and stress responses. Sperling et al., "Plant sphingolipids: structural diversity, biosynthesis, first genes and functions" *Biochimica et Biophysica Acta* 1632:1-15 (2003)

[0124] 1. Introduction

[0125] Sphingolipids are ubiquitous membrane components in eukaryotic cells and in a few bacteria. K. A. Karlsson, *Lipids* 5 (1970) 878-891; and K. A. Karlsson, *Chem. Phys. Lipids* 5 (1970) 6-43. Their chemical structure differs from the more commonly known glycerolipids in having a ceramide backbone, which consists of a fatty acid attached to a long-chain amino alcohol. Recent interest is focusing on the role of sphingolipids in serving as intra- and intercellular second messengers regulating cell growth, differentiation, apoptosis, and pathogenic defense. van Meer et al., *Biochim. Biophys. Acta* 1486 (2000) 145-170; and Dickson et al., *Biochim. Biophys. Acta* 1583 (2002) 13-25.

[0126] Compared to the tremendous research on bioactive sphingolipids in mammalian systems and *Saccharomyces cerevisiae* published during the last two decades, there is a paucity of studies using plant systems. Studies on sphingolipid metabolism in plants have focused on demonstrating and characterizing the in vitro activities of enzymatic steps in major pathways. D. V. Lynch, *Methods Enzymol.* 311 (2000) 130-149. The success in elucidating additional aspects of their metabolism and in recognizing functions are mainly due to the fact that genes controlling biosynthetic steps of sphingolipids have been identified only recently from plants and some other phyla.

[0127] In many studies, *S. cerevisiae* served as a model organism to study sphingolipid metabolism and may be the first eukaryotic organism in which all sphingolipid metabolic genes are identified. However, these data do not apply to the biosynthesis and functions of the structural diverse plant sphingolipids. For example, divergencies in the biosynthetic pathway of plants lead to cerebrosides and glycosyl inositol phosphorylceramides (GIPC) with a preference for D8-unsaturated long-chain bases (LCB) not present in baker's yeast. Imai et al., *Biosci. Biotechnol. Biochem.* 61 (1997) 351-353; Kawaguchi et al., *Biosci. Biotechnol. Biochem.* 64 (2000) 1271-1273; Imai et al., *J. Plant Physiol.* 157 (2000) 453-456; Mano et al., *Biosci. Biotechnol. Biochem.* 63 (1999) 619-626; Fujino et al., *J. Cereal Sci.* 1 (1983) 159-168; Ohnishi et al., *Biochim. Biophys. Acta* 752 (1983) 416-422; W. R. Morrison, *Chem. Phys. Lipids* 11 (1973) 99-102. Because cerebrosides and unsaturated LCB are absent in yeast, this organism has been used as an expression platform for heterologous genes involved in plant sphingolipid synthesis.

[0128] In this way, genes encoding enzymes modifying the ceramide core have been recently identified from a variety of different phyla including plants. Sperling et al., *J. Biol. Chem.* 273 (1998) 28590-28596; Sperling et al., *FEBS Lett.* 494 (2001) 90-94; Leipelt et al., *J. Biol. Chem.* 276 (2001) 33621-33629; Terries et al., *J. Biol. Chem.* 277 (2002) 25512-25518; and Mitchell et al., *J. Biol. Chem.* 272 (1997) 28281-28288. Sequence comparisons provide evolutionary relationships of some of these proteins. Sperling et al., *Prostaglandins Leukot. Essent. Fat. Acids* 68 (2003) 73-95. An extrapolation of the success with *S. cerevisiae* as a model suggests that the generation of plant mutants affecting sphingolipid metabolism will promote the elucidation of sphingolipid functions. For example, targeted gene disruption by homologous recombination established for: i) the moss *Physcomitrella patens* (Schafer et al., *Plant J.* 11 (1997) 1195-1206; and Girke et al., *Plant J.* 15 (1998) 39-48; ii) RNAi antisense inactivation (Mourrain et al., *Genet. Eng.* (New York) 22 (2000) 155-170; Wesley et al., *Plant J.* 27 (2001) 581-590); and iii) the identification of transposon-tagged *Arabidopsis thaliana* mutants (Bouche et al., *Curr. Opin. Plant Biol.* 4 (2001) 111-117; and Thorneycroft et al., *J. Exp. Bot.* 52 (2001) 1593-1601), may provide opportunities to identify and characterize new functions for plant sphingolipids. Structures of sphingolipids found in plants, comprise seemingly minor structural modifications as compared to other phyla which may have unexpected relevance on sphingolipid functions.

[0129] 2. Structural Diversity of Plant Sphingolipids

[0130] Sphingolipids are commonly generated by the addition of a polar head group to ceramides which in turn are composed of a 2-amino-1,3-dihydroxyalkane (LCB) moiety bonded to an N-acylated fatty acid (i.e., for example, comprising 14-26 carbon atoms). Complex sphingolipids, such as cerebrosides and GIPC (phytoglycolipids) may be formed by the addition of various glycosyl residues and other polar phosphate-containing headgroups to the ceramide. Depending on the source, this basic ceramide structure can be modified by differences in chain length, methyl branching, insertion of additional hydroxy groups, and degree of unsaturation.

[0131] 2.1. Long-Chain Bases

[0132] In mammals, the LCB moiety is mostly (E)-sphing-4-enine (sphingosine, $d18{:}1^{4}$), whereas in the yeast *S. cerevisiae*, the predominant LCB is 4-hydroxysphinganine (phytosphinganine, t18:0) formed by the desaturation or hydroxylation of sphinganine (d18:0) at C-4, respectively. In contrast, the sphingoid base composition of plants is more variable, being composed of up to eight different C18-sphingoid bases derived from D-erythro-sphinganine. See, FIG. **4**. Due to an additional cis- or trans-desaturation at C-8, the predominating regioisomers of unsaturated plant LCB are (E/Z)-sphing-8-enine ($d18:1^8$), (4E,8E/Z)-sphinga-4,8-dienine ($d18:2^{4,8}$) and (8E/Z)-4-hydroxy-8-sphingenine ($t18:1^8$), whereas $d18:1^4$ is virtually absent and d18:0 and t18:0 are only present in minor proportions. Other LCB differing in chain length are present as minor components in plant sphingolipids.

[0133] In *Euphorbia characias*, as well as in several other organisms, saturated and D6-(Z)-unsaturated tetrahydroxysphingenine derivatives may occur, suggesting the presence of an additional C5-LCB hydroxylase. Rupcic et al., *Chem. Phys. Lipids* 91 (1998) 153-161; and Li et al., *Tetrahedron Lett.* 36 (1995) 3875-3876. The occurrence of a D6-(Z)-double bond may be either due to the activity of an "exotic" LCB desaturase or to a serine palmitoyltransferase accepting D4-(Z)-myristoyl-CoA. The occurrence of D8-unsaturated LCB is not restricted to plants. For example, *S. cerevisiae* contain a di-unsaturated, methyl-branched LCB, (4E,8E)-9-methylsphinga-4,8-dienine in their cerebrosides. Toledo et al., *Biochemistry* 38 (1999) 7294-7306; Sakaki et al., *Yeast* 18 (2001) 679-695; Ohnishi et al., *J. Jpn. Oil Chem. Soc.* 45 (1996) 51-56; Abe et al., *Biosci. Biotechnol. Biochem.* 58 (1994) 1671-1674. In contrast, t18:0 is the predominating LCB in GIPC. Lester et al., *Adv. Lipid Res.* 26 (1993) 253-274; Jennemann et al., *Eur. J. Biochem.* 259 (1999) 331-338; Jennemann et al., *Eur. J. Biochem.* 268 (2001) 1190-1205.

[0134] As known so far, the occurrence of both D8 cis/transisomers seems to be restricted to plant sphingolipids. Ratios of D8-trans- to D8-cis-isomers varying from 91:9 in cucumber to 4:86 in wheat have been found in the leaf cerebrosides of different plant species. In *A. thaliana*, the (8Z)-t18:1 is the most abundant LCB in leaf cerebrosides recovered from lipid extracts, whereas direct alkaline hydrolysis of whole leaves indicates that the (8E)-t18:1 isomer is most abundant. Taking into account that GIPC are hardly extractable in organic solvents (i.e., for example, chloroform/methanol) which are suitable for the extraction of most membrane lipids including cerebrosides, these data suggest that other complex sphingolipids such as GIPC must be more abundant than monoglucosylceramides in *A. thaliana* leaves. Z. Imre, Z *Naturforsch.* 29c (1974) 195-200. The analysis of these complex phytoglycolipids is handicapped by complicated extraction and purification procedures and only a few plant GIPC have been analysed in detail. Carter et al., *Biochemistry* 8 (1969) 383-388; Kaul et al., *Plant Physiol.* 55 (1975) 120-129; Kaul et al., *Biochemistry* 17 (1978) 3569-3575; Hsieh et al., *Biochemistry* 17 (1978) 3575-3581; Hsieh et al., *J. Biol. Chem.* 256 (1981) 7747-7755; and Laine et al., *Methods Enzymol.* 138 (1987) 186-195. Therefore, at present, no exact data on the quantitative proportions of cerebrosides and GIPC in plants are available.

[0135] A comparison of the LCB compositions of *A. thaliana* leaves derived from lipid extracts (i.e., for example, a cerebroside fraction) and from lipid-depleted tissues (i.e., for example, a GIPC fraction) are pointing to a predominance of GIPC compared to cerebrosides and further suggests that there is a channeling of the (8Z)-t18:1 into cerebrosides and of the (8E)-isomer into GIPC. Furthermore, the relative proportions of di- and trihydroxybases in cerebrosides differ with plant species as well, for example, from 78% dihydroxybases in soybean to 87% trihydroxybases in *A. thaliana*, whereas the glucosylceramides of leaf and root tissues have similar LCB compositions. These studies suggest that plants maintain two separate ceramide pools for the biosynthesis of cerebrosides and GIPC, which could be achieved by different ceramide selectivities of glucosylceramide synthase (GCS) and inositol phosphorylceramide synthase or by restricting access of the enzymes to spatially separated substrate pools.

[0136] 2.2. Fatty Acyl Amides

[0137] In the ceramide backbones of plant sphingolipids, more than 10 different fatty acids can be N-acylated to the eight different LCB mentioned above. These fatty acids are almost exclusively α-D-hydroxylated and vary in their chain lengths from C_{14} to C_{26}, including chains of odd carbon numbers. Imai et al., *Biosci. Biotechnol Biochem.* 59 (1995) 1309-1313; Imai et al., *Lipids* 35 (2000) 233-236; and Bohn et al., *Arch. Biochem. Biophys.* 387 (2001) 35-40. Saturated C_{16}, C_{20}, C_{22} and C_{24} α-hydroxylated fatty acids are most abundant, whereas ω9-monounsaturated very long-chain fatty acids ranging from C_{22} to C_{26} occur in low proportions. The occurrence of 2-hydroxy nervonic acid (24h:1) is characteristic for the leaf cerebrosides of some chillingresistant cereals. Imai et al., In: J. P. Williams, M. U. Khan, N. W. Lem (Eds.), Physiology, Biochemistry and Molecular Biology of Plant Lipids, Kluwer Academic Publishing, Dordrecht, 1997, pp. 224-226.

[0138] The occurrence of ω9-cis-unsaturated very long-chain fatty acyl amide residues in sphingolipids may be attributed to the sequential fatty acid elongation of oleoyl-CoA resulting in a series of ω9-monounsaturated very long-chain fatty acyl-CoA of 22-26 carbons which could serve as substrate for the plant ceramide synthase. In free ceramides, non-hydroxylated fatty acids can account for 1-32%, whereas in leaf cerebrosides, they are minor constituents ranging from 1% to 3%. Cahoon et al., *Plant Physiol.* 95 (1991) 58-68; and Ohnishi et al., *Agric. Biol. Chem.* 46 (1982) 2855-2856. In several plants, even 2-3% of 2,3-dihydroxy fatty acids have been detected, suggesting the existence of a regio-unselective acyl amide α-hydroxylase or of a C3-hydroxylase. Ito et al., *Agric. Biol. Chem.* 49 (1985) 539-540; and Ohnishi et al., *Agric. Biol. Chem.* 49 (1985) 3327-3329.

[0139] In yeast GIPC, fatty acids of 26 carbons in length are predominating, the majority of which is hydroxylated at the α-position. Lester et al., *J. Biol. Chem* 268 (1993) 845-856; and Nurminen et al., *Biochem. J.* 125 (1971) 963-969. The presence of 2,3-dihydroxy acids has been described in N-acyl-4-hydroxysphinganine isolated from *S. cerevisiae*, whereas a Δ3-(E)-unsaturation of 2-hydroxy fatty acids appears to be a modification restricted to some fungal cerebrosides. Prostenik et al., *Lipids* 8 (1973) 325-326; Weinert et al., *Chem. Phys. Lipids* 11 (1973) 83-88; Fujino et al., *Biochim. Biophys. Acta* 486 (1976) 161-171; and Ballio et al., *Biochim. Biophys. Acta* 573 (1979) 51-60.

[0140] These data indicate not only the presence of an acyl amide C3-hydroxylase in plant and baker's yeast, but also of an acyl amide Δ3-(E)-desaturase in some pathogenic fungi. The corresponding genes coding for these modifications at C-3 have not been identified.

[0141] 2.3. Polar Head Group

[0142] Studies on the molecular species of ceramide residues show that almost all possible combinations of LCB and fatty acids occur in nature giving rise to two types of complex plant sphingolipids. See, FIG. **5**. In plants, neutral cerebrosides carry one to four glycosyl residues attached to the primary hydroxyl group of the sphinganine derivatives, whereas in the negatively charged GIPC (phytoglycolipids), inositol-1-phosphate is linked as a phosphodiester to C-1 of the ceramide backbone, which may be further extended by oligosaccharide chains. GPIC core structure nor biosynthesis analyses has been studied in detail in plants.

[0143] There are at least two different monoglycosyl ceramides in plants carrying either β-D-mannosyl- or β-D-glucosyl residues. The glucosylceramide is mainly used for further β(1→4) linked mannosylations resulting in series of di-, tri- and tetraglycosyl ceramides, which are terminally capped by a glucosyl residue apparently preventing further chain elongation. Fujino et al., *Proc. Jpn. Acad.* 58B (1982) 36-39; and Fujino et al., *Agric. Biol. Chem.* 49 (1985) 2753-2762. Therefore, it seems unlikely that the cellobiosyl ceramide may act as a primer for cellulose synthesis as proposed for β-sitosterol glucosides in plants. Peng et al., *Science* 295 (2002) 147-150. More than 20 different glucosylceramide species with 12 species comprising each more than 1 mol % of the total cerebroside mixture have been determined in some plant species. For example, galactosyl ceramides (i.e, for example, neuraminic (sialic) acid containing ceramides (e.g., gangliosides)) and sphingomyelin, all of which are typical mammalian sphingolipids, have not been found in higher plants. Huwiler et al., *Biochim. Biophys. Acta* 1485 (2000) 63-99. In plants, the glucosylceramides typically account for less than 5 mol % of the total lipids, but are quantitatively important components of the outer (apoplastic) monolayer of the plasma membrane comprising 7-30 mol % of membrane lipids. Lynch et al., In: J.-C. Kader, P. Mazliak (Eds.), Plant Lipid Metabolism, Kluwer Academic Publishing, Dordrecht, 1995, pp. 239-241. On the other hand, the bilayer distribution of sphingolipids in the tonoplast has not been determined yet. The same is true for the intracellular location and transbilayer distribution of GIPC in plants. The sum of both, cerebrosides and GIPC, may be significantly higher than anticipated. If they are concentrated in one leaflet of bilayer membranes, the proportion of phospholipids would be significantly reduced.

[0144] 3. Characterization of Plant Genes for Sphingolipid Biosynthesis

[0145] A potential pathway for sphingolipid synthesis in plants has been proposed. See, FIG. **6**. The identified orthologous plant genes are indicated by black boxed enzyme names. Sequences identified in the genome of *A. thaliana* are included and are marked by black dots.

[0146] 3.1. Ceramide Synthesis

[0147] Sphingolipid biosynthesis starts with the condensation of acyl-CoA (mainly palmitoyl-CoA) and L-serine to yield 3-ketosphinganine, catalyzed by the palmitoyl-CoA:L-serine C-palmitoyltransferase (EC 2.3.1.50). Detection of this enzyme activity in plant microsomes by in vitro assays points to a localization in the endoplasmic reticulum (ER). The reaction can be specifically inhibited by L-cycloserine, β-chloro-L-alanine and by the antifungal agents sphingofungin B and C. Zweerink et al., *J. Biol. Chem.* 267 (1992) 25032-25038. As shown for the yeast enzyme, the serine palmitoyltransferase from plants may also consist of two essential subunits, Lcb1 and Lcb2. Gable et al., *J. Biol. Chem.* 275 (2000) 7597-7603.

[0148] An LCB2 cDNA from *A. thaliana* has been functionally expressed in a yeast mutant defective in serine palmitoyltransferase activity. Tamura et al., *Plant Cell Physiol.* 42 (2001) 1274-1281. Expression of a green-fluorescent protein fusion product in tobacco cells showed that Lcb2 is localized in the endoplasmic reticulum (ER). Inspection of the complete *Arabidopsis* genome database suggests a second hypothetical LCB2-like gene (AB074928) and a putative LCB1-like gene (AB063254). The serine palmitoyltransferase has a strong preference for palmitoyl-CoA, but also palmitelaidoyl-CoA with a trans-double bond at C-9, was still an effective substrate. Saturated acyl-CoAs of shorter or longer chain length as well as palmitoleoyl-CoA with a cis-double bond at C-9 were highly discriminated. Lynch et al., *Plant Physiol.* 103 (1993) 1421-1429. The specificity of the plant serine palmitoyltransferase for unsaturated C_{18} acyl-CoA such as oleic-, linoleic- or linolenic-CoA representing the main fatty acyl residues in plants, has not been investigated.

[0149] It has been shown, that very long-chain polyunsaturated fatty acids such as eicosapentaenoic acid (20:5) produced by the fungus *Mortierella alpina* are not incorporated into its cerebrosides. Batrakov et al., *Chem. Phys. Lipids* 117 (2002) 45-51. In a second step, 3-ketosphinganine is reduced with NADPH by the D-erythro-sphinganine:NADP$^+$ 3-oxidoreductase (EC 1.1.1.102) to yield sphinganine (D-erythro-2-amino-1,3-dihydroxyalkane). The TSC10 gene encoding this membrane-bound and essential enzyme in *S. cerevisiae* has been located at the cytosolic side of the ER in mammalian cells. Beeler et al., *J. Biol. Chem.* 273 (1998) 30688-30694; and Mandon et al., *J. Biol. Chem.* 267 (1992) 11144-11148.

[0150] Two homologs encoding putative 3-ketosphinganine reductases (Accession Numbers NM_111481 and NM_121925) can be found in the *A. thaliana* genome, but their functions have not been identified. In the next step, the amino group of sphinganine is acylated to yield ceramide (N-acyl sphinganine). In yeast, this reaction is catalysed by two similar acyl-CoA:sphinganine N-acyltransferases (ceramide synthases, EC 2.3.1.24), Lac1 and Lag1, requiring long chain acyl-CoA. Schorling et al., *Mol. Biol. Cell* 12 (2001) 3417-3427; and Guillas et al., *EMBO J.* 20 (2001) 2655-2665. Two cDNA homologs of LAG1 (AF198179, AF198180) may code for two putative sphinganine N-acyltransferases in *A. thaliana*. Brandwagt et al., *Proc. Natl. Acad. Sci. U.S.A.* 97 (2000) 4961-4966. The activity of such an enzyme has been demonstrated in microsomal membranes of squash, bean and corn, suggesting a localization in ER membranes.

[0151] D-Erythro-sphinganine and -sphingosine serve as substrates for the N-acyltransferase, whereas DL-threo-sphinganine and 4-hydroxysphinganine do not. In yeast, the ceramide synthases obviously channel C_{26} fatty acids into GIPC. In plants, the distribution of hydroxy fatty acyl chains in glucosylceramides is paralleled by the substrate specificity of the enzymes using C_{16} to C_{24} acyl-CoA. These data suggest a role for this enzyme in determining the acyl amide compositions of both cerebrosides and GIPC. Hydroxy acyl chains do not function as substrate, indicating that α-hydroxylation apparently occurs following ceramide formation.

[0152] The second mechanism for ceramide synthesis utilizing predominantly free palmitic acid in plants has been demonstrated in vitro. Ceramidase activity is stimulated by the addition of erythro-sphinganine, whereas (E)-sphing-4-enine is a poor substrate and 4-hydroxysphinganine inhibits ceramide formation. In yeast, two ceramidases preferring either N-acyl sphinganine, Ydc1, or N-acyl 4-hydroxysphinganine, Ypc1, have been cloned. From these two enzymes, Ypc1 is probably involved in sphingolipid degradation, showing acyl-CoA-independent reverse activity in ceramide formation. Mao et al., *J. Biol. Chem.* 275 (2000) 6876-6884;

and Mao et al., *J. Biol. Chem.* 275 (2000) 31369-31378. A putative ceramidase is also present in *A. thaliana*, but the YPC1 gene (BAB60897) has not been cloned. Comparison of the in vitro activities of the sphinganine N-acyltransferase and the reverse ceramidase in plant membrane preparations indicates that ceramide formation in vivo may occur predominantly by the acyl-CoA dependent reaction. The role of the reverse ceramidase in vivo remains unclear, though it may act as salvage mechanism for otherwise cytotoxic free fatty acids and LCB.

[0153] 3.2. Modifications of the Hydrophobic Ceramide Core

[0154] Once the ceramide backbone is established, the LCB and acyl amide residues are further modified by desaturations and/or hydroxylations to form the molecular species commonly found in plants. Only a few enzymatic activities required for these modifications have been demonstrated in vitro, and the true substrates for these reactions, that is, free LCB, ceramide, cerebroside or GIPC, are still not known with certainty.

[0155] 3.2.1. C4-LCB Hydroxylation

[0156] In plants, sphinganine can be either desaturated to (E)-sphing-4-enine or it can be C_4-hydroxylated to yield 4-hydroxysphinganine (phytosphinganine), most of which is further desaturated to yield cis/trans-isomers of Δ8-unsaturated LCB. Laine et al., *Biochemistry* 12 (1973) 1106-1111. In *S. cerevisiae*, lacking Δ4-LCB desaturation, a non-essential SUR2/SYR2 gene responsible for C4-LCB hydroxylation to give C_{18}- and C_{20}-phytosphinganine has been identified by gene disruption. Haak et al., *J. Biol. Chem.* 272 (1997) 29704-29710; and Grilley et al., *J. Biol. Chem.* 273 (1998) 11062-11068. It is unclear whether sphinganine, N-acyl-sphinganine (dihydroceramide) or both are substrates for hydroxylation at C-4. SUR2-orthologous sequences have been found in *Schizosaccharomyces pombe, Candida albicans* and *A. thaliana*. Heterologous expression of each of two Sur2-like genes identified from *A. thaliana* in a sur2Δ-null mutant lacking C4-LCB-hydroxylation resulted in the formation of D-ribo-C_{18}- and —C_{20}-phytosphinganine indicating the presence of two isoenzymes for C4-LCB hydroxylation.

[0157] 3.2.2. Δ4-LCB Desaturation

[0158] Plants are believed to synthesize sphingolipids with Δ4-transunsaturated LCB. Laine et al., *Biochemistry* 12 (1973) 1106-1111. In mammals, the Δ4-(E)-desaturation occurs at the cytosolic face of ER membranes at the level of N-acyl sphinganine. Causeret et al., *Lipids* 35 (2000) 1117-1125. NADH or NADPH and molecular oxygen are required as co-factors, whereas cyanide, divalent copper, dithiothreitol and antibodies raised against cytochrome b5 inhibit sphingolipid Δ4-(E)-desaturase (dihydroceramide desaturase) activity. Factors that influence the mammalian enzyme activity include the alkyl chain length of the LCB ($C_{18}>C_{12}>C_8$), the acyl amide chain ($C_8>C_{18}$), the stereochemistry of the LCB (D-erythro>L-threo-N-acyl sphinganines) and the nature of the headgroup with highest activity observed with N-acyl sphinganine, some with dihydrosphingomyelin, but no activity with free C_{18}-sphinganine or dihydroglucosylceramide. Michel et al., *J. Biol. Chem.* 272 (1997) 22432-22437.

[0159] Plant orthologous Δ4-(E)-desaturase sequences have been found in *A. thaliana* (AF220201) and *Lycopersicon esculentum*. Both the sphingolipid Δ4-(E)-desaturase as well as the SUR2-like C4-hydroxylase sequences show three conserved histidine motifs characterizing all membrane-bound fatty acyl desaturases. Shanklin et al., *Annu. Rev. Plant Physiol. Plant Mol. Biol.* 49 (1998) 611-641. But both sequences do not contain a cytochrome b5 domain, which inter alia has been found in sphingolipid Δ8-desaturases and some acyl amide α-hydroxylases. Sperling et al., *Eur. J. Lipid Sci. Technol.* 103 (2001) 158-180.

[0160] 3.2.3. Δ8-LCB Desaturation

[0161] Like Δ4-(E)-desaturation, Δ8-unsaturated sphingolipids do not occur in baker's yeast. Interestingly, only the transisomers of Δ8-unsaturated LCB have been found in *Pichia pastoris, Rhynchosporium secalis, M. alpina* and other fungi, whereas a mixture of cis- and trans-isomers is characteristic for plants. For example, genes encoding plant sphingolipid Δ8-desaturases (EC 1.14.99) have been functionally identified from *A. thaliana, Brassica napus, Helianthus annuus* and *Borago officinalis*. Sperling et al., *Biochem. Soc. Trans* 28 (2000) 638-641; Sperling et al., *Arch. Biochem. Biophys.* 388 (2001) 293-298. Surprisingly, heterologous expression of these cDNA sequences in *S. cerevisiae* resulted in significant proportions of both cis- and transisomers of plant characteristic 4-hydroxysphing-8-enines not present in wild-type yeast cells.

[0162] The presence of C_{18}- and C_{20}-(8E/Z)-4-hydroxysphing-8-enines in these transgenic cells can be ascribed to the activity of a stereounselective sphingolipid Δ8-desaturase lacking absolute chain length specificity. Depending on the plant source, different and characteristic E/Z-ratios ranging from 3:1 to 7:1 were obtained when using the same yeast expression system. Any influence from an unspecific yeast isomerase could be excluded because wild-type yeast incorporating exogenously applied, synthetic Δ6-(E)-hexadecenoic acid into sphingolipids yielded exclusively (E)-4-hydroxyshing-8-enine and do not show any conversion to the (Z)-isomer. The formation of both (E)- and (Z)-double bonds results from a syn-elimination of two vicinal hydrogen atoms from two different substrate conformers. Beckmann et al., *Angew. Chem. Int. Ed. Engl.* 41 (2002) 2298-2300. Low but distinct kinetic isotopic effects suggest a preferential attack at C-8 of 4-hydroxysphinganine with anti-orientation en route to the E-isomer and at C-9 with gauche-orientation to the Z-isomer. Since both isomers are generated by the same enzyme, a uniform mechanism involving a transient C-centered radical can be proposed. Therefore, the sphingolipid Δ8-desaturase is different from the hitherto studied and stereospecifically operating fatty acyl (Z)-desaturases including the sphingolipid Δ4-(E)-desaturase from rat, which all attack a hydrogen at the carbon atom proximal to the polar head. Behrouzian et al., *Curr. Opin. Chem. Biol.* 6 (2002) 577-582.

[0163] The plant sphingolipid Δ8-desaturases tested in a yeast sur2Δ-mutant strain cultured with or without 4-hydroxysphinganine required a C4-hydroxylated substrate, suggesting that Δ8-desaturation followed C4-hydroxylation to yield (8E/Z)-4-hydroxysphing-8-enines. However, nonhydroxylated (Z)- and (E)-sphing-8-enines are present in plant glucosylceramides which may point to a second sphingolipid D8-desaturase activity in plants required for the synthesis of (4E,8E/Z)-sphing-4,8-dienines. In fact, a second sphingolipid D8-desaturase sequence is present in *B. officinalis* and in *A. thaliana* (Accession Number NM_130183). Expression of this second *A. thaliana* cDNA in a *S. cerevisiae* sur2Δ-mutant strain revealed a similar C4-hydroxy-preference of the enzyme, although traces of sphing-8-enine were also formed. These data are consistent with the high proportions of Δ8-unsaturated trihydroxybases but minor proportions of

Δ8-unsaturated dihydroxybases present in *A. thaliana* sphingolipids. Recently, expression of a sphingolipid Δ8-desaturase from *Aquilegia vulgaris* in *S. cerevisiae* and in a sur2Δ-mutant showed that this enzyme is able to use both 4-hydrosphinganine and sphinganine as substrates, respectively. Michaelson et al., *Biochem. Soc. Trans.* 30 (2001) 1073-1075.

[0164] The LCB composition of this member of the Ranunculaceae has not been analysed yet. Therefore, it may be speculated that plant species containing higher proportions of (E/Z)-sphing-8-enine and (4E,8E/Z)-sphing-4,8-dienine express Δ8-desaturase isoenzymes differing in their selectivity for 4-hydroxysphinganine and sphinganine. Interestingly, expression of a moss cDNA in *S. cerevisiae* resulted in the first identification of a cis-specific sphingolipid Δ8-desaturase using 4-hydroxysphinganine as substrate. Furthermore, the activity of this Δ8-(Z)-desaturase is significantly increased in the presence of glucosylceramide. However, in plants, the sequence of hydroxylation and desaturation to form 4-hydroxysphing-8-enines and sphinga-4,8-dienes remains to be elucidated.

[0165] The sphingolipid D8-desaturase sequences identified in plants and fungi all show the histidine box motifs characteristic for membrane-bound desaturases and their desaturase domain is N-terminally fused to cytochrome b5. The identification of this N-terminal domain from sunflower has been confirmed by expression of the recombinant protein domain in exhibiting redox absorbance spectra characteristic for plant microsomal cytochrome b5.

[0166] 3.2.4. Acyl Amide Hydroxylation

[0167] Sphingolipids from plants usually contain α-hydroxylated fatty acids. Evidence for a direct α-hydroxylation of fatty acyl residues when bound as elements of intact sphingolipids or free ceramide came from radiolabeling studies of *Tetrahymena pyriformis*. Kaya et al., *J. Biol. Chem.* 259 (1984) 3548-3553. A non-essential acyl amide α-hydroxylase gene, FAH1 or SCS7, respectively, has been identified in *S. cerevisiae* by gene disruption/deletion leading to a significant reduction in 2-hydroxylated cerotic acid (26h:0).

[0168] Database searches revealed orthologous sequences from *S. pombe, Caenorhabditis elegans* and *A. thaliana*. Heterologous expression of one of the two *A. thaliana* homologs found in the genome (i.e., for example, Accession Number AY050326), led to a significant increase in 26h:0 in a fah1D yeast mutant strain. Whether the second homolog (i.e., for example, Accession Number AY058151) codes for an isoenzyme of the acyl amide 2-hydroxylase or for a 3-hydroxylase, responsible for the formation of 2,3-hydroxylated acyl amides as mentioned above, remains to be determined. Interestingly, the yeast and *C. elegans* protein sequences each showed a N-terminal cytochrome b5-fusion which is lacking in the *A. thaliana* and *S. pombe* orthologs.

[0169] 3.2.5. Phylogenetic Relationships

[0170] The four different groups of enzymes (i.e., for example, acyl amide ahydroxylase, LCB C4-hydroxylase, LCB Δ4-(E)-desaturase, or LCB Δ8-(E/Z)-desaturase) modifying the hydrophobic ceramide core may belong to a large superfamily of membrane bound proteins including, but not limited to, fatty acid desaturases involved in the biosynthesis of polyunsaturated fatty acids. These oxygen-dependent enzymes are characterized by three conserved histidine motifs which may be involved in binding a di-iron complex.

[0171] A phylogram derived from amino acid alignments of these sphingolipid desaturases and hydroxylases shows four distinct branches originating in the middle of the phylogram which indicates a very early separation of these paralogous groups. See, FIG. **7**. It is assumed that enzymes with identical or similar regioselectivity are also similar in their amino acid sequence. Sperling et al., *Eur. J. Biochem.* 267 (2000) 3801-3811. Sphingolipid Δ8-desaturases are more similar to fatty acyl Δ5- and Δ6-desaturases all of which are cytochrome b5 fusion proteins and have evolved independently of sphingolipid Δ4-desaturase activity. Napier et al., *Trends Plant Sci.* 4 (1999) 2-4. Interestingly, the fatty acyl lipid Δ4-desaturase, which recently has been cloned from *Thraustochytrium* sp. and which is also a cytochrome b5-fusion protein, is also more similar to the fatty acyl Δ5/Δ6-desaturases than to the non-fused sphingolipid Δ4-desaturase and C4-hydroxylase. Qiu et al., *J. Biol. Chem.* 276 (2001) 31561-31566. Thus, Δ4/C4-regioselectivity must have evolved independently three times pointing to a convergent evolution of fatty acyl Δ4-desaturase, sphingolipid Δ4-desaturase and sphingolipid C4-hydroxylase. The invariant fusion between sphingolipid Δ8-desaturases and cytochrome b5 which represents the immediate electron donor for many microsomal desaturases, may have a functional advantage.

[0172] 3.3. Formation of Complex Sphingolipids

[0173] One possible modification of the primary hydroxyl group of ceramides occurs by glycosylation yielding cerebrosides. cDNAs coding for UDP-glucose:ceramide β-D-glucosyltransferase (GCS) have not been found in either *S. cerevisiae* or *S. pombe* which is consistent with the lack of cerebrosides in these yeasts. Ichikawa et al., *Proc. Natl. Acad. Sci. U.S. A.* 93 (1996) 4638-4643; Takakuwa et al., *FEMS Yeast Res.* 2 (2002) 533-538; and Leipelt et al., *Biochem. Soc. Trans.* 28 (2000) 751-752. Recently, a plant GCS has been identified from *Gossypium arboreum* (cotton) by its functional expression in *P. pastoris* showing similarity to a putative GCS sequence (Accession Number AF424585) in *A. thaliana*. There is only little information on the substrate specificity of plant GCS. Studies on the mammalian enzyme showed that it requires UDP-glucose and N-acyl-D-erythrosphinganine and that it does not accept the L-erythro enantiomer or the L-threo diastereomer. Venkataraman et al., *Biochim. Biophys. Acta* 1530 (2001) 219-226. Unexpectedly, an in vitro assay using microsomal membranes from bean hypocotyls and radiolabeled sterol glucoside as substrate demonstrated UDP-glucose-independent GCS activity. Lynch et al., *Arch. Biochem. Biophys.* 340 (1997) 311-316. The assumption that sterol glucoside may function as a glucosyl donor is in line with recent data that sterol glucosides act as primers for cellulose synthesis in plants. Read et al., *Science* 295 (2002) 59-60. In contrast, a sterol glucosyltransferase/GCS double null-mutant of *P. pastoris* expressing the cotton GCS resulted in sterol glucoside-independent glucosylceramide synthesis, suggesting that UDP-glucose is the actual sugar donor. The presence of an N-terminal transmembrane domain and the sterol glucoside-independency of the plant enzyme supports a location in the Golgi apparatus as suggested for the mammalian enzyme rather than an exoplasmic orientation in the plasma membrane. Cantatore et al., *Biochem. Soc. Trans.* 28 (2000) 748-750.

[0174] Expression of the cotton GCS in a *P. pastoris* GCS-null mutant resulted in characteristic glucosylceramide species with non- and α-hydroxylated C_{16}- to C_{24}-acyl amides, suggesting that in fungi, initial Δ4-(E)-desaturation is followed by Δ8-(E)-desaturation and final C9-methylation of the LCB. The fact that (4E,8E)-9-methyl-sphinga-4,8-dienine is the major LCB in free ceramides of several fungi supports the assumption that ceramide glycosylation succeeds LCB modifications. Yaoita et al., *Chem. Pharm. Bull.* (*Tokyo*) 50 (2002) 681-684. However, it is not clear whether in plants, cerebroside formation occurs before or after the modifications of the hydrophobic ceramide core.

[0175] The formation of other complex plant sphingolipids such as mannosylceramide and GIPC is still unclear, because no gene coding for a mannosylceramide synthase or for an inositol phosphorylceramide synthase has been identified in plants yet. In *S. cerevisiae*, the first step in GIPC formation is catalyzed by the posphatidylinositol:ceramide phosphoinositol transferase (IPC synthase) which transfers the inositol-phosphate moiety from phosphatidylinositol to the C-1 hydroxy group of ceramide. Becker et al., *J. Bacteriol.* 142 (1980) 747-754. The membrane-bound enzyme has been shown to be located in the Golgi apparatus of *S. cerevisiae*. Levine et al., *Mol. Biol. Cell* 11 (2000) 2267-2281. IPC synthase activity is inhibited by antifungal agents such as aureobasidin A, khafrefungin and rustmycin. In *S. cerevisiae*, the IPC synthase or a subunit of the enzyme is encoded by the AUR1 gene. Hashida-Okado et al., *Mol. Gen. Genet.* 251 (1996) 236-244; Nagiec et al., *J. Biol. Chem.* 272 (1997) 9809-9817. Surprisingly, a similar gene cannot be found in the *A. thaliana* genome or in other plant genomes such as rice, wheat, barley and oat. Due to the lack of any in vitro and in vivo studies or data concerning the effectiveness of the antifungal IPC synthase inhibitors in plant systems, there is no evidence for the existence of an IPC synthase in plants. Therefore, in plants, either a completely different (insensitive) protein or a different reaction mechanism may be involved in this step.

[0176] 4. Functions of Sphingolipids in Plants

[0177] There is still little information on the functions of sphingolipids in plants. However, functions including, but not limited to, cell signaling, membrane stability, stress response, pathogenesis and apoptosis have been suggested.

[0178] 4.1. Cell Signaling

[0179] Sphingolipids are thought to be cellular mediators not only in animals and fungi, but also in plants. For example, a knock-out of an *A. thaliana* gene coding for a protein accelerating in vitro (E)-sphing-4-enine transfer between membranes caused activation of cell death and defense-related genes. Brodersen et al., *Genes Dev.* 16 (2002) 490-502. Evidence for the presence of (E)-sphing-4-enine-1-phosphate in plants has been achieved showing its involvement in drought-induced signal transduction in guard cells linking the perception of abscisic acid to a reduction in turgor. Ng et al., *Nature* 410 (2001) 596-599. Furthermore, sphing-4-enine-1-phosphate promoting Ca^{2+}-mediated guard cell closure required the presence of the Δ4-double bond. Therefore, the low abundance of sphing-4-enine in plant sphingolipids does not indicate its biological insignificance, but may point either to a selective incorporation into rare sphingolipids or to an exclusive occurrence in specific tissues or cell types, respectively. Sphingolipids may further play a role in the establishment and maintenance of cell polarity via control of the actin cytoskeleton and that accumulation of ceramide and is likely responsible for arresting the cell cycle in G1.

[0180] 4.2. Membrane Stability

[0181] Sphingolipids may also be important for plant membrane organization. Mammalian and fungal sphingolipids have a tendency to associate with cholesterol or ergosterol, respectively, and form clusters of raft-like domains, which are important for lateral sorting of proteins, cellular trafficking and signal transduction. R. T. Dobrowsky, *Cell. Signal.* 12 (2000) 81-90; van Meer et al., *J. Biol. Chem.* (2002) 25855-25858; and Simons et al., *Nat. Rev. Mol. Cell Biol.* 1 (2000) 1-39. Plasma membrane microdomains exist in plant cells as well, although they contain sterols other than cholesterol. Peskan et al., *Eur. J. Biochem.* 267 (2000) 6989-6995. The plant-specific sterols sitosterol and stigmasterol, differing in aliphatic side chain structure from cholesterol, by an additional ethyl group at C-24 and the latter by an additional Δ22-(E)-double bond, also promote domain formation, which is modulated by sterol side chain structure. Xu et al., *J. Biol. Chem.* 276 (2001) 33540-33546. Moreover, small amounts of free ceramide significantly stabilize domain formation, suggesting that this signaling molecule is likely to concentrate within sphingolipid/sterol rafts. The presence of GPI-anchored proteins in plants have lead to the identification of a COB(RA)-like multigene family in *A. thaliana* encoding putative GPI-anchored proteins, which may be involved in orientated cell expansion at the plasma membrane-cell wall interface of vascular plants.

[0182] 4.3. Abiotic Stress Response

[0183] Sphingolipids have been implicated in conferring stability to plant membranes, contributing to acclimation to drought stress and to cold hardiness in chilling resistant plants Lynch et al., *Plant Physiol.* 83 (1987) 761-767; Bohn, PhD thesis, Faculty of Biology, University of Hamburg, Hamburg, Germany, (1999). It has been observed that the proportion of glucosylceramides in plasma membranes of freezing-tolerant plants is lower than in freezing-sensitive plants and that the glucosylceramide content is reduced following cold acclimation. The molecular species composition of cerebrosides differed among chilling-sensitive and -tolerant plants and changed during cold acclimation. Among many plant species analysed, hydroxy nervonic acid (24h:1) was only found in the leaf cerebrosides of chilling-resistant plants, suggesting that cerebroside species with monounsaturated very long-chain hydroxy acyl amides exhibit much lower phase transitions than those having a saturated hydroxy acyl amide residue. Furthermore, most of the chilling-resistant plant species analysed had more 8-(Z)-unsaturated than 8-(E)-trihydroxy-bases, suggesting that high levels of (8E/Z)-4-hydroxysphing-8-enine are correlated with freezing tolerance.

[0184] 4.4. Phytopathogenesis

[0185] A new field of sphingolipid functions comprises plant-pathogen interactions. For example, certain cerebrosides isolated from plants stimulate fruiting body formation of *Schizophyllum commune*, a fungus involved in wood degradation. The active glucosylceramides from wheat grain consisted of α-hydroxylated C_{16}- or C_{18}-acyl amides, and of (4E,8Z)-sphinga-4,8-dienine or (Z)-sphinga-8-enine. Kawai et al., *J. Biol. Chem.* 261 (1986) 779-784. Hydrogenation of the (Z)-sphinga-8-enine containing glucosylceramide showed that the stimulatory effect of these cerebrosides was dependent on the presence of a 48-double bond. More recent studies showed that fungal cerebrosides function as elicitors causing hypersensitive cell death, phytoalexin accumulation and increased resistance to subsequent infections by compatible pathogens in plants. Elicitor-active glucosylceramides were isolated from the rice pathogenic fungus *Magnaporthe grisea* having an amide-linked (3E)-2-hydroxyhexadec-3-enoyl or (3E)-2-hydroxyoctadec-3-enoyl group bound to (4E, 8E)-9-methyl-sphinga-4,8-dienine. Interestingly, hydrogenation of the Δ8-(E)-double bond in the LCB or of the Δ3-

(E)-double bond in the acyl amide moiety of the cerebroside did not alter elicitor activity, whereas the Δ4-(E)-double bond of the LCB and the methyl group at C-9 were essential for elicitor activity. The glucose headgroup was not crucial, because free ceramide also showed elicitor activity though with reduced effectiveness In field experiments with application of as little as 3×45 g/ha, these glucosylceramide elicitors, which occur in many different phytopathogens, protected rice plants against *M. grisea* and other diseases as well, indicating that cerebrosides function as general elicitors in a wide range of rice-pathogen interactions. The importance of the Δ8-double bond in fungal fruiting body induction or of the Δ4-double bond and 9-methyl group in the hypersensitive response to phytopathogens indicates that diverse structural LCB modifications are contributing to different cellular responses in plant-pathogen interactions. The observation of an increase in the expression of serine palmitoyltransferase during the hypersensitive response of a late-blight-resistant potato to *Phytophthora infestans* also points to the involvement of sphingolipids in pathogenesis. Koga et al., *Biol. Chem.* 273 (1998) 31985-31991; Uemura et al., *Plant Cell Physiol.* 41 (2000) 676-683; Uemura et al., *Plant Cell Physiol.* 43 (2002) 778-784; Birch et al., *Mol. Plant-Microb. Interact.* 12 (1999) 356-361.

[0186] 4.5. Programmed Cell Death

[0187] Sphingolipids may be involved in plant apoptosis and ceramide signalling as sphinganine-analogous mycotoxins (SAMs) such as fumonisins produced by *Fusarium moniliforme* and related fungi, and host-selective toxins secreted from *Alternaria alternate* f sp. *Lycopersici* (AAL), have been shown to be cytotoxic and cancerogenic in animals. SAMs have been shown to induce necrosis, DNA fragmentation and accumulation of free LCB in different plant tissues. Siler et al., *Physiol. Mol. Plant Pathol.* 23 (1983) 265-274; Abbas et al., *Plant Physiol.* 106 (1994) 1085-1093; Wang et al., *Plant Cell* 8 (1996) 375-391; Moore et al., *Physiol. Mol. Plant Pathol.* 54 (1999) 73-85. These results could be attributed to a competitive inhibition of the sphinganine N-acyltransferase (ceramide synthase) activity. Merrill Jr., et al., In: D. E. Vance, J. E. Vance (Eds.), Biochemistry of Lipids, Lipoproteins and Membranes, vol. 31, Elsevier, Amsterdam, 1996, pp. 309-339; D. G. Gilchrist, *Cell Death Differ.* 4 (1997) 689-698; P. V. Minorsky, *Plant Physiol.* 129 (2002) 929-930.

[0188] In tomato, co-dominant insensivity to SAMs is believed mediated by the ASC1 gene (Alternaria stem canker), which is homologous to the yeast longevity assurance gene (LAG1) and facilitates the ER-to-Golgi transport of GPI-anchored proteins. Overexpression of Asc1 in SAM-sensitive plants resulted in resistance to infection by *A. alternata* f sp. *lycopersici*, indicating that susceptibility of tomatoes for SAMs may involve sphingolipids and ER-to-Golgi transport of GPI-anchored proteins. Labeling experiments of Asc/Asc and asc/asc tomato leaf discs with tritiated serine indicated that the presence of Asc1 is able to relieve an AAL toxin-induced block of sphingolipid synthesis that otherwise would lead to programmed cell death. Spassieva et al., *Plant J.* 32 (2002) 561-572.

[0189] B. Morphine Analgesia and Sphingolipids

[0190] Morphine and many other opioid agonists have analgesic effects that are believed to be mediated by their activation of inhibitory opioid receptors on nociceptive (pain-mediating) neurons. Accordingly, these opioids are administered to relieve severe pain. Morphine and many other opioid agonists, however, also have been shown to activate excitatory opioid receptors on nociceptive neurons, thereby attenuating the analgesic potency of the opioid agonists, and resulting in the development of anti-analgesia, hyperexcitability, hyperalgesia, physical dependence, psychological dependence, tolerance, and other adverse (excitatory) effects Crain et al.," Opioids can evoke direct receptor-mediated excitatory effects on sensory neurons" *Trends in Pharmacol. Sci.,* 11:77-81 (1990). Consequently, a long-standing need has existed to develop a method which will both enhance the analgesic (inhibitory) effects of these bimodally-acting opioid agonists and block or prevent adverse (excitatory) effects associated with their administration.

[0191] It has been reported that the analgesic potency of bimodally-acting opioid agonists can be enhanced, and the tolerance/dependence liability reduced, by co-administering bimodally-acting opioid agonists with ultralow doses of selective excitatory opioid receptor antagonists (e.g., U.S. Pat. Nos. 5,472,943; 5,512,578; 5,580,876; and 5,767,125, all herein incorporated by reference). Excitatory opioid receptor antagonists are compounds that bind to and inactivate excitatory opioid receptors, but not inhibitory opioid receptors, on neurons in nociceptive (pain) pathways. Selective excitatory opioid receptor antagonists attenuate excitatory, but not inhibitory, opioid receptor functions in nociceptive pathways of the peripheral and central nervous systems. As a result, symptoms associated with activation of excitatory opioid receptors (e.g., anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, and tolerance effects) are blocked, while the analgesic effects of the bimodally-acting opioid agonists, which are mediated by the inhibitory opioid receptors, are unmasked and thereby enhanced. Crain et al., "Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine on sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment" *Proc. Natl. Acad. Sci. USA,* 92:540-544 (1995); Crain et al., "GM1 ganglioside-induced modulation of opioid receptor-mediated functions" *Ann. N.Y. Acad. Sci.,* 845:106-125 (1998); Crain et al., "Modulation of opioid analgesia, tolerance and dependence by G_s-coupled, GM1 ganglioside-regulated opioid receptor functions" *Trends in Pharmacol. Sci.,* 19:358-65 (1998). These preclinical studies have suggested that ultralow doses of selective excitatory opioid receptor antagonists can be administered alone to chronic pain patients to enhance the analgesic potency and reduce the tolerance/dependence liability of endogenous opioid peptides, such as enkephalins, dynorphins, and endorphins, which are elevated in chronic pain patients.

[0192] It has also been reported that ultralow doses of naltrexone, alone or in combination with low-dose methadone (e.g., U.S. Pat. No. 5,512,578, herein incorporated by reference), and ultralow doses of other excitatory opioid receptor antagonists alone (e.g., U.S. Pat. Nos. 5,580,876 and 5,767,125, both herein incorporated by reference), can provide effective, long-term maintenance treatment for opioid addiction after acute detoxification, and can prevent relapse to drug abuse.

[0193] GM1 is a monosialoganglioside that is abundantly distributed on the external surface of neuronal cell membranes. Fishman, P. H., "Gangliosides and cell surface receptors and transducers of biological signals" In: New Trends in Ganglioside Research: Neurochemical and Neuroregenerative Aspects, R. W. Ledeen, E. L. Hogan, G. Tettamenti, A. J.

Yates, and R. K. Yu (eds.) (Padova: Liviana, 1988) pp. 183-201. GM1-ganglioside plays a role in regulating excitatory opioid receptors in nociceptive neurons, probably by binding to an allosteric regulatory site on opioid receptors. Shen et al., "Cholera toxin-B subunit blocks opioid excitatory effects on sensory neuron action potentials indicating that GM1 ganglioside may regulate G_s-linked opioid receptor functions" *Brain Res.* 531:1-7 (1990); and Shen et al., "Brief treatment of sensory ganglion neurons with GM1 ganglioside enhances the efficacy of opioid excitatory effects on the action potential" Brain Res., 550:130-138 (1991). Other data have suggested that the analgesic potency of opioid agonists is enhanced, and the tolerance/dependence liability of endogenous opioid peptides is reduced, when opioids are co-administered with high doses of exogenous GM1-ganglioside. Mao et al., "Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C" *J. Neurosci.* 14:2301-2312 (1994); Mayer et al., "The development of morphine tolerance and dependence is associated with translocation of protein kinase C" *Pain* 61:365-374 (1995); U.S. Pat. Nos. 5,321,012; 5,502,058; 5,556,838; and 5,654,281 (all herein incorporated by reference).

[0194] In contrast, it has demonstrated that intraperitoneal (i.p.) injection of low doses of exogenous GM1-ganglioside (0.1 mg/kg) in mice rapidly attenuates morphine's analgesic effects. Crain et al., "Enhanced analgesic potency and reduced tolerance of morphine in 129/SvEv mice: evidence for a deficiency in GM1 ganglioside-regulated excitatory opioid receptor functions" *Brain Res.,* 856:227-235 (2000). As a result, it was suggested that the analgesic potency of morphine may be increased upon co-administration with cholera toxin B (CTX-B) or oseltamivir. Both these agents inhibit specific functions of endogenous GM1-ganglioside on opioid receptors in nociceptive neurons. Crain et al. "Methods for increasing analgesic potency and attenuating adverse excitatory effects of bimodally-acting opioid agonists by inhibiting GM1-ganglioside" United States Patent Application 2002/0137761. Cholera toxin consists of a non-covalently-assembled pentamer of a non-toxic B subunit (CTX-B) that is responsible for cell attachment, and a toxicogenic A subunit (CTX-A). Mekalanos et al., "Cholera toxin gene: nucleotide sequence, deletion analysis and vaccine development" *Nature,* 306:551-557 (1983). CTX-B binds selectively to GM1-ganglioside on the surface of cells, and facilitates penetration of CTX-A into the cell membrane. Gill, D. M., "Mechanism of action of cholera toxin" *Adv. Cycl. Nucl. Res.,* 8:85-118 (1977).

[0195] Oseltamivir is an ethyl ester pro-drug that requires ester hydrolysis for conversion to the active form, oseltamivir carboxylate. The proposed mechanism of action of oseltamivir is via inhibition of influenza-virus neuraminidase, with the possibility of alteration of virus particle aggregation and release. Oseltamivir and its analogues and derivatives are available commercially. Oseltamivir is prepared in tablet form, for oral administration, under the trademark Tamiflu®, and may be obtained from Roche Laboratories (Nutley, N.J.). Tamiflu® is available as a capsule containing 75 mg of oseltamivir for oral use, in the form of oseltamivir phosphate. Tamiflu® may be administered to a subject in a dose ranging from 0.1-1 mg/kg, once or twice a day.

[0196] Oseltamivir at doses that result in neuraminidase inhibition of influenza virus also may be effective in decreasing GM1-ganglioside levels in nociceptive neurons. Such a decrease in levels of GM1-ganglioside would result in attenuation of the efficacy of GM1-regulated, G_s-coupled, excitatory opioid receptor-mediated hyperalgesic functions, thereby unmasking G_i/G_o-coupled inhibitory opioid receptor-mediated analgesia and reducing development of tolerance and physical dependence. Gubareva et al., "Influenza virus neuraminidase inhibitors" *Lancet* 355:827-835 (2000).

[0197] Previous studies have shown that pretreatment of dorsal root ganglion (DRG) neurons with CTX-B selectively blocks opioid-induced prolongation of the action potential duration (APD), but not opioid-induced shortening of the APD, suggesting that GM1-ganglioside may regulate G_s-linked excitatory opioid receptor functions in DRG neurons. Shen et al., "Cholera toxin-B subunit blocks opioid excitatory effects on sensory neuron action potentials indicating that GM1 ganglioside may regulate G_s-linked opioid receptor functions" *Brain Res.,* 531:1-7 (1990). Additional studies on DRG neurons in culture have shown that chronic opioid treatment, together with administration of nanomolar concentrations of CTX-B, prevents development of tolerance to the inhibitory, APD-shortening effects of micromolar concentrations of the opioid, by preventing the development of opioid excitatory supersensitivity (i.e., for example, a cellular manifestation related to opioid tolerance and dependence in vivo). Shen et al., "Chronic selective activation of excitatory opioid receptor functions in sensory neurons results in opioid "dependence" without tolerance" *Brain Res.,* 597:74-83 (1992). CTX-B blockade appears to involve interference with GM1-ganglioside regulation of opioid excitatory receptor functions. In particular, it was reported that CTX-B binds with selective high affinity ($K_D=10^{-10}$ M) to GM1-ganglioside. Wu et al., "The role of GM1 ganglioside in regulating excitatory opioid effects" *Ann. N.Y. Acad. Sci.,* 845:126-138 (1998). Treatment of DRG neurons with anti-GM1 antibodies has been shown selectively to block opioid-induced APD prolongation, as occurs with CTX-B. Shen et al., "Cholera toxin-B subunit blocks opioid excitatory effects on sensory neuron action potentials indicating that GM1 ganglioside may regulate G_s-linked opioid receptor functions" *Brain Res.,* 531:1-7 (1990).

[0198] Gangliosides are a class of galactose-containing complex glycolipids (i.e., for example, sphingolipids). Gangliosides are found in highest concentration in the nervous system, particularly in gray matter, where they constitute 6% of the lipids. In gangliosides, an oligosaccharide chain containing at least one acidic sugar is attached to ceramide. The acidic sugar is N-acetylneuraminate or N-glycolylneuraminate, both of which are sialic acids. GM1 is a monosialoganglioside that is abundantly distributed on the external surface of neuronal cell membranes. It is formed by the addition of N-acetylgalactosamine and a galactose group.

[0199] Neuraminidase also regulates cellular levels of GM1-ganglioside. For example, administration of exogenous neuraminidase has been shown markedly to increase the concentrations of GM1-ganglioside in cell membranes of DRG cells and other neurons by enzymatic removal of neuraminic (sialic) acid from polysialylated ligands of the gangliotetraose series. Wu et al., "Stimulation of neurite outgrowth in neuroblastoma cells by neuraminidase: putative role of GM1 ganglioside in differentiation" *J. Neurochem.* 56:95-104 (1991); and Wu et al., "GM1 ganglioside modulates prostaglandin E1 stimulated adenylyl cyclase in neuro-2A cells" *Glycoconjugate J.,* 13:235-239 (1996); , 64, 65, 69). This specific effect of neuraminidase on the enzymatic conversion of polysialylated gangliosides to GM1-ganglioside in neurons is quite distinct from the roles of neuraminidase in promoting release of influenza virus from infected cells and in facilitating virus spread within the respiratory tract.

[0200] In one embodiment, an agent that inhibits GM1-ganglioside in nociceptive neurons may be a neuraminidase inhibitor, including, but not limited to, $MgSO_4$, Na_2SO_4, oseltamivir, or zanamivir. For example, Na_2SO_4 may be administered to a subject in need of treatment for pain in an amount on the order of 10 mg/kg per day.

VII. Pharmaceutical Formulations

[0201] The present invention further provides pharmaceutical compositions (e.g., comprising the Kratom-dervied compounds described above). The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration.

[0202] Pharmaceutical compositions and formulations for topical administration may include, but are not limited to, transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

[0203] Compositions and formulations for oral administration include, but are not limited to, powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets or tablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable.

[0204] Compositions and formulations for parenteral, intrathecal or intraventricular administration may include, but are not limited to, sterile aqueous solutions that may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

[0205] Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids.

[0206] The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0207] The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

[0208] In one embodiment of the present invention the pharmaceutical compositions may be formulated and used as foams. Pharmaceutical foams include formulations such as, but not limited to, emulsions, microemulsions, creams, jellies and liposomes. While basically similar in nature these formulations vary in the components and the consistency of the final product.

[0209] The compositions of the present invention may additionally contain other adjunct components conventionally found in pharmaceutical compositions. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like.

[0210] Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. The administering physician can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual compounds, and can generally be estimated based on EC_{50}'s found to be effective in in vitro and in vivo animal models or based on the examples described herein. In general, dosage is from 0.01 mg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly. The treating physician can estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the subject undergo maintenance therapy to prevent the recurrence of the disease state, wherein the compound is administered in maintenance doses, ranging from 0.01 μg to 100 g per kg of body weight, once or more daily, to once every 20 years.

EXPERIMENTAL

Example I

Withdrawal from Hydromorphone Addiction

[0211] This example shows that long-term Kratom use promotes extinction of opioid cravings in a middle aged male, who, after transitioning without withdrawal from injection hydromorphone use to Kratom administration. The patient was adminstered Kratom for three years and subsequently terminated Kratom use without a taper (i.e., for example, a successive reduction in daily dose to effectively zero). The patient did not exhibit any symptoms of opioid withdrawal except for rhinorrhea.

[0212] A 43-year-old male was admitted for evaluation of a generalized tonic-clonic seizure. The patient's medical history included chronic pain from thoracic outlet syndrome that was being treated with hydromorphone. As hydromorphone-induced tolerance escalated, the patient began injecting 10 mg hydromorphone per day (S.C.) from crushed pills. When hydromorphone was unavailable, the patient purchased Kratom (i.e., for example, from internet vendors) and self-administered the compound (~$15K per year).

[0213] Following one such abrupt hydromorphone cessation (3.5 years before seeking professional substance abuse treatment) the patient averted opioid withdrawal by ingesting a tea made from Kratom four times a day. The patient attributed substantial pain relief to Kratom as well as improved alertness and did not experience drowsiness often accompanied by opioid use.

[0214] The patient then co-administered 100 mg modafinil with Kratom in an attempt to further improve alterness. Twenty minutes following this co-admininstration, he experienced a generalized tonic-clonic seizure lasting 5 minutes. Vital signs at presentation were: pulse 123 beats per minute, blood pressure 130/74 mm/Hg, respiratory rate 16; he was afebrile. After a brief post-ictal period, his physical examination was normal except for meiosis. He had no previous history of seizures or head trauma, and he denied alcohol or recent illicit drug abuse. Laboratory studies were unremarkable; qualitative urine drugs of abuse and comprehensive toxicology screening identified only modafinil. Computerized tomography and magnetic resonance imaging of the brain were normal. We identified no adulterants or contaminants. Upon discharge, the patient abruptly ceased use of Kratom and sought the care of an addiction specialist.

[0215] This withdrawal from Kratom was considerably less intense, but more protracted, than that previously experienced from prescription opioids. Physician-observed features of Kratom included rhinorrhea, insomnia, poor concentration, constricted affect and myalgias persisting for 10 days from his last dose of kratom. To prevent relapse, an addiction specialist prescribed buprenorphine/naloxone, reaching a maintenance dose of 16 mg per day. Rhinorrhea ceased on the first day of suboxone therapy.

[0216] The patient currently reports adequate pain control, and follow-up urine screens for drugs of abuse have remained negative. We confirmed the identity of the plant matter ingested by the patient as Kratom by comparison against a known standard (Pure Land Ethnobotanicals, Madison, Wis., USA) utilizing existing extraction and high-performance liquid chromatography protocols.

Example II

Mitragynine Pharmacokinetics

[0217] After a 12 h fast, rats (n=8 per sampling time) received by gavage a single oral dose of 20 mg/kg mitragynine dissolved in 1% acetic acid pH 4.7 (adjusted with 1M NaOH solution).[39] Heparinzed blood samples were collected at times zero, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 15, 24 and 48 hr after administration of the drug; detection was performed using liquid chromatography-tandem mass spectroscopy with electrospray interface.

[0218] Pharmacokinetic parameters were calculated based on the plasma concentration versus time curves using WinNonlin version 4.0 program using first-order kinetics, a monocompartment model and no lag time. The experimental data were analyzed statistically using the Graphpad Instat® software for the calculation of mean, median, and 95% confidence interval. The obtained pharmacokinetic data is presented graphically. See, FIG. **2**.

Example III

Validation Of Mitragynine Detection and Stability

[0219] The method developed for detection of mitragynine has been validated by evaluating recovery, linearity, precision, accuracy, quantification limit, and stability. The coefficient of variation and relative error values at the three concentrations were obtained in the intra- and inter-day assays. See, FIG. **3**. The results show that the analytical method is accurate (±15% different from the nominal concentration) and the precision values expressed as coefficient of variation are within the accepted limits of 15% or less for the concentration levels studied. Furthermore, tests of short-term (4 h at room temperature), freeze-thaw (3 cycles) and post-processing (16 h at 12° C.) stabilities demonstrated sample stability with no variation of more than 15% at any of the concentrations tested.

Example IV

Effects of Kratom Extracts on Morphine Withdrawal Symptoms

[0220] In this experiment mice were chronically administered either morphine using an increasing dose paradigm starting at 20 mg/kg and ending at 100 mg/kg (i.p.) or a saline vehicle control for six days. Subsequent to the morphine administration the mice were administered either: i) Kratom tea extract (1 g/kg; p.o.); ii) Kratom tea extract (2 g/kg; p.o.); iii) methadone (23 mg/kg; p.o.); iv) methadone (100 mg/kg; p.o.); or v) mitragynine (23 mg/kg; p.o.) for another six days. Morphine withdrawal symptoms were initiated by the injection of naloxone (10 mg/kg; i.p.). Kratom extract and mitragyine reduced naloxone-precipitated morphine withdrawal symptoms in a similar manner as methadone. The Kratom extract administrations demonstrated a dose-dependent effect.

TABLE 1

Effect of oral administration of lyophilized tea extract of *Mitragyna speciosa* and pure mitragynine on precipitation of morphine withdrawal symptoms.

Morphine (20-100 mg/kg) (i.p.) + Compound + 10 mg/kg Naloxone (i.p.)	Locomotor Activity	Jumping Frequency	Paw Tremor Frequency	Wet Dog Shakes Frequency	Teeth Chattering Frequency	Last Day % Weight Control
Saline (i.p)	3793 ± 150.0	2.700 ± 0.9551	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	107.2 ± 1.393
Morphine (i.p.)	1870 ± 114.2***	21.6 ± 4.378***	156.2 ± 7.124***	9.433 ± 1.334***	76.10 ± 6.572***	89.64 ± 0.6012***
1 g/kg Kratom Tea Extract (p.o.)	2441.0 ± 222.4***$^{\#}$	0.00 ± 0.00$^{\#\#\#}$	9.667 ± 2.102$^{\#\#\#}$	10.78 ± 2.379***	0.8889 ± 0.6111$^{\#\#\#}$	96.61 ± 2.264***$^{\#\#\#}$
2 g/kg Kratom Tea Extract (p.o.)	3045 ± 191.8*$^{\#\#\#}$	1.300 ± 0.5588$^{\#\#\#}$	3.200 ± 1.123$^{\#\#\#}$	7.500 ± 0.9339*	0.00 ± 0.00$^{\#\#\#}$	92.92 ± 2.326***
23 mg/kg Methadone (p.o.)	1866 ± 225.9***	0.00 ± 0.00$^{\#\#\#}$	110.7 ± 8.809***$^{\#\#\#}$	5.600 ± 0.9684*	81.20 ± 8.704***	100.1 ± 0.8121$^{\#\#\#}$
100 mg/kg Methadone (p.o.)	2512 ± 131.5***$^{\#}$	1.111 ± 0.7536$^{\#\#\#}$	8.444 ± 1.692$^{\#\#\#}$	0.6667 ± 0.3333$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	100.1 ± 1.205$^{\#\#\#}$
23 mg/kg Mitragynine (p.o.)	2485 ± 119.1***$^{\#}$	0.00 ± 0.00$^{\#\#\#}$	3.200 ± 0.7424$^{\#\#\#}$	0.6000 ± 0.2667$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	101.3 ± 0.8619$^{\#\#\#}$

*$p < 0.05$,
**$p < 0.001$,
***$p < 0.0001$ verses Saline control (Dunnett's post hoc test)
$^{\#}p < 0.05$,
$^{\#\#}p < 0.001$,
$^{\#\#\#}p < 0.0001$ verses Morphine control (Dunnett's post hoc test)

[0221] The control values for each compound administered in combination with naloxone is shown in Table 2.

TABLE 2

Effect of oral administration of lyophilized tea extract of *Mitragyna speciosa* and pure mitragynine followed by naloxone administration in comparison to morphine and methadone

Compound + 10 mg/kg Naloxone (i.p.)	Locomotor Activity	Jumping Frequency	Paw Tremor Frequency	Wet Dog Shakes Frequency	Teeth Chattering Frequency	Last Day % Weight Control
Saline (i.p.)	3616 ± 172.9	1.600 ± 0.8844	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	103.6 ± 1.566
Morphine (i.p.)	1870 ± 114.2***	21.6 ± 4.378***	156.2 ± 7.124***	9.433 ± 1.334***	76.10 ± 6.572***	89.64 ± 0.6012***
Naloxone (i.p.)	3291 ± 145.3$^{\#\#\#}$	1.800 ± 0.9978$^{\#\#\#}$	3.800 ± 0.9978$^{\#\#\#}$	0.6000 ± 0.3399$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	99.94 ± 1.225$^{\#\#\#}$
1 g/kg Kratom Tea Extract (p.o.)	2792 ± 181.6$^{\#\#\#}$	0.0700 ± 0.4726$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	100.9 ± 1.786$^{\#\#\#}$
2 g/kg Kratom Tea Extract (p.o.)	2747 ± 172.9**$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	1.800 ± 0.9978***	8.800 ± 2.641***	0.00 ± 0.00$^{\#\#\#}$	92.39 ± 1.710***
23 mg/kg Methadone (p.o.)	2595 ± 288.4**$^{\#}$	0.00 ± 0.00$^{\#\#\#}$	6.400 ± 1.462$^{\#\#\#}$	2.000 ± 0.5164$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	96.64 ± 1.046*
100 mg/kg Methadone (p.o.)	2.886 ± 228.4*$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	5.000 ± 1.549$^{\#\#\#}$	1.900 ± 0.5859$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	98.30 ± 0.6976$^{\#\#\#}$
23 mg/kg Mitragynine (p.o.)	3010 ± 108.1$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	1.800 ± 0.6464$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	0.00 ± 0.00$^{\#\#\#}$	98.85 ± 0.8938$^{\#\#\#}$

TABLE 2-continued

Effect of oral administration of lyophilized tea extract of *Mitragyna speciosa* and pure mitragynine followed by naloxone administration in comparison to morphine and methadone

Compound + 10 mg/kg Naloxone (i.p.)	Locomotor Activity	Jumping Frequency	Paw Tremor Frequency	Wet Dog Shakes Frequency	Teeth Chattering Frequency	Last Day % Weight Control
Vehicle (1:1:18) (p.o.)	3172 ± $189.7^{\#\#\#\#}$	0.00 ± $0.00^{\#\#\#\#}$	2.300 ± $0.6839^{\#\#\#\#}$	0.9000 ± $0.3480^{\#\#\#\#}$	0.00 ± $0.00^{\#\#\#\#}$	99.66 ± $0.9439^{\#\#\#\#}$

*$p < 0.05$,
**$p < 0.001$,
***$p < 0.0001$ verses Saline control (Dunnett's post hoc test)
$^{\#}p < 0.05$,
$^{\#\#}p < 0.001$,
$^{\#\#\#}p < 0.0001$ verses Morphine control (Dunnett's post hoc test)

I claim:

1. A method, comprising:
a) providing,
i) a subject experiencing at least one withdrawal symptom induced by at least one addictive compound;
ii) a Kratom extract capable of reducing or preventing said at least one withdrawal symptom; and
b) administering said Kratom extract to said subject under conditions such that said at least one withdrawal symptom is prevented or reduced.

2. The method of claim **1**, wherein said addictive compound comprises an opiate compound.

3. The method of claim **1**, wherein said addictive compound comprises a cannabinoid compound.

4. The method of claim **1**, wherein said addictive compound comprises an ethanol compound.

5. The method of claim **1**, wherein said addictive compound comprises a cocaine compound.

6. The method of claim **2**, wherein said opiate compound comprises a prescribed opiate compound.

7. The method of claim **1**, wherein said Kratom extract comprises mitragynine.

8. The method of claim **1**, wherein said Kratom extract comprises a mitragynine derivative.

9. The method of claim **8**, wherein said mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine.

10. The method of claim **1**, wherein said withdrawal symptom comprises a craving induced by said addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

11. A method, comprising:
a) providing,
i) a subject repeatedly exposed to at least one addictive compound, wherein said subject is at risk of experiencing at least one withdrawal symptom;
ii) a composition comprising mitragynine, wherein said composition is capable of reducing or preventing said at least one withdrawal symptom; and
b) administering said composition to said subject under conditions such that said at least one withdrawal symptom is prevented or reduced.

12. The method of claim **11**, wherein said administering further comprises a regimen of decreasing said composition comprising mitragynine over a predetermined length of time.

13. The method of claim **11**, wherein said addictive compound comprises an opiate compound.

14. The method of claim **11**, wherein said addictive compound comprises a cannabinoid compound.

15. The method of claim **11**, wherein said addictive compound comprises an ethanol compound.

16. The method of claim **11**, wherein said addictive compound comprises a cocaine compound.

17. The method of claim **13**, wherein said opiate compound comprises a prescribed opiate compound.

18. The method of claim **11**, wherein said composition comprises a mitragynine derivative.

19. The method of claim **18**, wherein said mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine.

20. The method of claim **11**, wherein said withdrawal symptom comprises a craving induced by said addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

21. A method, comprising:
a) providing;
i) a subject repeatedly exposed to at least one addictive opioid compound, wherein said subject is at risk of experiencing at least one opioid withdrawal symptom;
ii) a composition comprising mitragynine, wherein said composition is capable of reducing or preventing said at least one withdrawal symptom; and
administering said composition to said subject under conditions such that said at least one withdrawal symptom is prevented and/or reduced.

22. The method of claim **21**, wherein said administering further comprises a regimen of decreasing said composition comprising mitragynine over a predetermined length of time.

23. The method of claim **21**, wherein said opiate compound comprises a prescribed opiate compound.

24. The method of claim **21**, wherein said composition further comprises a mitragynine derivative.

25. The method of claim **24**, wherein said mitragynine derivative comprises mitragynine pseudoindoxyl or 7-hydroxymitragynine.

26. The method of claim **21**, wherein said withdrawal symptom comprises a craving induced by said addictive compound binding to a receptor selected from the group consisting of mu-, delta-, or kappa-opiate receptor.

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